THIETANE 1,1-DIOXIDES AS POTENTIAL ANALGETICS
OF THE METHADONE TYPE

by

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ABSTRACT

Thietane derivatives containing phenyl and dimethylaminomethyl substituents were synthesized as potential narcotic analgetics of the methadone type. These compounds which are structurally derived from the sulfone analogue of methadone by joining C-2 to C-5, are conformationally more restricted than methadone and thus may be useful in elucidating the conformation of methadone when bound to its receptor (pharmacophoric conformation).

The photocycloaddition reaction of thiobenzophenone and an appropriate olefinic nitrile provided 2,2-diphenyl-3-cyanothietane, cis-2,2-diphenyl-3-cyano-4-methylthietane and trans-2,2-diphenyl-3-cyano-4-methylthietane, cis-2,2-diphenyl-3-methyl-4-cyanothietane and trans-2,2-diphenyl-3-methyl-4-cyanothietane. Treatment of the first three thietane derivatives with m-chloroperbenzoic acid gave 2,2-diphenyl-3-cyanothietane 1,1-dioxide, cis-2,2-diphenyl-3-cyano-4-methylthietane 1-oxide, cis-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide and trans-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide. Submitting the cyanothietane 1,1-dioxides to hydroboration reduction gave the corresponding primary amines which were catalytically dimethylated with formaldehyde at room temperature to give 2,2-diphenyl-3-dimethylaminomethylthietane 1,1-dioxide, cis-2,2-di-
phenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide and trans-2,2-diphenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide.

Two attempts to synthesize the precursors of thietane derivatives containing a dimethylaminomethyl side chain attached to the carbon α to the sulfonyl group gave unexpected results. The reaction of β-chloroethane-sulfonyl chloride and β-dimethylaminostyrene generated an acyclic sulfone, α-(vinylsulfonyl)-β-dimethylaminostyrene, instead of the expected cyclic adduct, 2-phenyl-3-dimethylamino-4-chloromethylthietane 1,1-dioxide. The reported reaction of methoxyallene and thiobenzophenone to give 2,2-diphenyl-3-methoxy-4-methylenethietane was found to proceed in a different course. The reaction was proved to occur thermally as opposed to a photochemical reaction.

During the course of the studies, several reactions were performed on 2,4-diphenylthiete 1,1-dioxide with a hope of generating 2,4-diphenylthietan-3-one 1,1-dioxide for antiinflammatory studies:

Treating 2,4-diphenylthiete 1,1-dioxide with sodium hydroxide resulted in the cleavage of the thietane ring and formation of dibenzyl sulfone. The expected product, 2,2-diphenyl-3-hydroxythietane 1,1-dioxide was likely formed but rapidly underwent ring cleavage to give dibenzyl sulfone.

The reaction of 2,2-diphenylthiete 1,1-dioxide
with concentrated sulfuric acid resulted in formation of two rare compounds, \(3,2\)-5-diphenyl-1,6-2-oxathiacyclo-
penta-3-ene 2-oxide and \(3,6\)-5-diphenyl-1,6-2-oxathiacyclo-
penta-3-ene 2-oxide. This reaction did not occur with 2-
phenylthietene 1,1-dioxide and 2-phenyl-4-methylthietene 1,1-
dioxide.

None of three compounds tested showed significant analgesic activity in an in vitro experiment based on the inhibition of the contractions of electrically stimulated guinea-pig ileum by narcotic analgetics. In an in vivo experiment, the compounds were also unable to modify the pain threshold of a rabbit towards electrical stimulation on tooth-pulp. The results indicate the exacting requirement for binding of methadone to the narcotic receptor.

Signature of Supervisor
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>ABSTRACT</th>
<th>iii</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>THIETANE CHEMISTRY</td>
<td>26</td>
</tr>
<tr>
<td>SYNTHETIC APPROACH</td>
<td>60</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>63</td>
</tr>
<tr>
<td>1. Synthesis of cyanothietanes by photocycloaddition of thiobenzophenone with olefinic nitriles</td>
<td>63</td>
</tr>
<tr>
<td>2. Synthesis of cyanothietane 1,1-dioxides</td>
<td>76</td>
</tr>
<tr>
<td>3. Synthesis of 3-aminomethylthietane 1,1-dioxides</td>
<td>84</td>
</tr>
<tr>
<td>4. Synthesis of 3-dimethylaminomethylthietane 1,1-dioxides</td>
<td>92</td>
</tr>
<tr>
<td>5. Synthesis of 2,2-diphenyl-3-dimethylaminomethylthietane</td>
<td>100</td>
</tr>
<tr>
<td>6. Attempted synthesis of thietane derivatives with α-dimethylaminomethyl side chain</td>
<td>105</td>
</tr>
<tr>
<td>7. Chemical reactions of 2,4-diphenylthietane 1,1-dioxide and attempted synthesis of 2,4-diphenylthietan-3-one 1,1-dioxide</td>
<td>118</td>
</tr>
<tr>
<td>PHARMACOLOGICAL TESTING</td>
<td>143</td>
</tr>
<tr>
<td>PARTITION STUDIES</td>
<td>150</td>
</tr>
<tr>
<td>STRUCTURE-ACTIVITY CONSIDERATIONS</td>
<td>159</td>
</tr>
<tr>
<td>ANALYTICAL METHODS</td>
<td>166</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>167</td>
</tr>
<tr>
<td>1. Synthesis of thiobenzophenone (95)</td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>Synthesis of 2,2-diphenyl-3-cyano-thietane (155)</td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>2</td>
<td>Synthesis of 2,2-diphenyl-3-cyano-thietane 1,1-dioxide (160)</td>
</tr>
<tr>
<td>3</td>
<td>Synthesis of 2,2-diphenyl-3-amino-methylthietane 1,1-dioxide (161)</td>
</tr>
<tr>
<td>4</td>
<td>Synthesis of 2,2-diphenyl-3-dimethyl-aminomethylthietane 1,1-dioxide (32)</td>
</tr>
<tr>
<td>5</td>
<td>Synthesis of cis- and trans-2-butenenitriles</td>
</tr>
<tr>
<td>6</td>
<td>Synthesis of cis-2,2-diphenyl-3-cyano-4-methylthietane (156) and cis-2,2-diphenyl-3-methyl-4-cyano-thietane (158)</td>
</tr>
<tr>
<td>7</td>
<td>Synthesis of cis-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide (174)</td>
</tr>
<tr>
<td>8</td>
<td>Synthesis of cis-2,2-diphenyl-3-cyano-4-methylthietane 1-oxide (178)</td>
</tr>
<tr>
<td>9</td>
<td>Synthesis of cis-2,2-diphenyl-3-amino-methyl-4-methylthietane 1,1-dioxide (179)</td>
</tr>
<tr>
<td>10</td>
<td>Synthesis of cis-2,2-diphenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide (33)</td>
</tr>
<tr>
<td>11</td>
<td>Synthesis of trans-2,2-diphenyl-3-cyano-4-methylthietane (157) and trans-2,2-diphenyl-3-methyl-4-cyano-thietane (159)</td>
</tr>
<tr>
<td>12</td>
<td>Synthesis of trans-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide (176)</td>
</tr>
<tr>
<td>13</td>
<td>Synthesis of trans-2,2-diphenyl-3-aminomethyl-4-methylthietane 1,1-dioxide (180)</td>
</tr>
<tr>
<td>14</td>
<td>Synthesis of trans-2,2-diphenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide (34)</td>
</tr>
<tr>
<td>15</td>
<td>Synthesis of trans-2,2-diphenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide (34)</td>
</tr>
<tr>
<td>PAGE</td>
<td>16. Synthesis of 2,2-diphenyl-3-di-methylaminomethylthietane (191)</td>
</tr>
<tr>
<td></td>
<td>17. Synthesis of N,N-dimethylallylamine (200)</td>
</tr>
<tr>
<td></td>
<td>18. Attempted photocycloaddition of thio-benzophenone (95) to N,N-dimethyl-allylamine (200)</td>
</tr>
<tr>
<td></td>
<td>19. Synthesis of β-chloroethanesulfonfyl chloride (212)</td>
</tr>
<tr>
<td></td>
<td>20. Reaction of β-chloroethanesulfonfyl chloride (212) and β-dimethylamino-styrene (213)</td>
</tr>
<tr>
<td></td>
<td>21. Synthesis of methyl propargyl ether (218)</td>
</tr>
<tr>
<td></td>
<td>22. Synthesis of methoxyallene (113)</td>
</tr>
<tr>
<td></td>
<td>23. Synthesis of 2,2-diphenyl-3-methoxy-4-methylenethietane (114)</td>
</tr>
<tr>
<td></td>
<td>24. Attempted hydroxylation of 2,4-diphenylthiete 1,1-dioxide (227) with sodium hydroxide. Isolation of diphenylsulfone (234)</td>
</tr>
<tr>
<td></td>
<td>25. Reaction of 2,4-diphenylthiete 1,1-dioxide (227) with sulfuric acid. Isolation of 3,5-diphenyl-1,2-oxathiacyclopenta-3-ene 2-oxide (243, 244)</td>
</tr>
<tr>
<td></td>
<td>26. Attempted hydroboration of 2,4-diphenylthiete 1,1-dioxide (227)</td>
</tr>
<tr>
<td></td>
<td>27. Synthesis of 2,2-dichlorophenylacetyl chloride (282)</td>
</tr>
<tr>
<td></td>
<td>28. Synthesis of N,N-diethyl-2,2-dichlorophenylacetamide (283)</td>
</tr>
<tr>
<td></td>
<td>29. Synthesis of N,N-diethyl-α,β-dichloro-β-styrylamine (284)</td>
</tr>
<tr>
<td></td>
<td>30. Synthesis of N,N-diethylphenyl-</td>
</tr>
</tbody>
</table>
ethynylamine (285) ......................... 208

31. Synthesis of 2,4-diphenyl-3-diethyl-
aminothiete 1,1-dioxide (231) ............ 209

32. Attempted hydrolysis of 2,4-diphenyl-
3-diethylaminothiete 1,1-dioxide
(231) ........................................ 210

BIBLIOGRAPHY ........................................ 212
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Description</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Analgesic activities of methadone and its sulfone analogue in mice</td>
<td>12</td>
</tr>
<tr>
<td>II.</td>
<td>Vicinal coupling constants $J(\text{Ha-Hb})$ of 2,2-diphenylthietane derivatives</td>
<td>97</td>
</tr>
<tr>
<td>III.</td>
<td>Vicinal coupling constants of thietane derivatives</td>
<td>98</td>
</tr>
<tr>
<td>IV.</td>
<td>Chemical shifts of sulfonyl enamines</td>
<td>111</td>
</tr>
<tr>
<td>V.</td>
<td>Chemical shifts of sultines</td>
<td>135</td>
</tr>
<tr>
<td>VI.</td>
<td>Rm values of thietane 1,1-di-oxides at 0% methyl ethyl ketone calculated from regression lines</td>
<td>153</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Analgesic receptor surface proposed by Beckett and Casy</td>
<td>17</td>
</tr>
<tr>
<td>II. Pmr spectrum of cis-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide dissolved in CDCl$_3$</td>
<td>79</td>
</tr>
<tr>
<td>III. Inhibition of contractions of electrically stimulated guinea-pig ileum by methadone and thietane 1,1-dioxides</td>
<td>148</td>
</tr>
<tr>
<td>IV. Effect of methadone, thietane 1,1-dioxides and naloxone on guinea-pig ileum contractions</td>
<td>149</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

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DEDICATION

To my wife, Li-Tchou
INTRODUCTION

Thousands of morphine-like compounds have appeared in the literature. To date, the majority of synthetic analgesics which are as active as morphine in relieving pain are all associated with tolerance and addiction. Extensive efforts of medicinal chemists are needed to design an analgesic molecule without these undesirable properties.

Morphine (1) is a derivative of phenanthrene (2) bridged by oxygen and nitrogen across the 4, 5 and 9, 13 positions respectively. The natural morphine, isolated from opium, occurs as a levo isomer. The piperidine ring D adopts
a chair conformation, while the cyclohexene ring C is in a boat form with a C/D ring junction trans, rings C and B being cis-fused. The phenolic ring A is connected to ring D by an axial C-13 bond and an axial C-9 methylene bridge. Expanding the phenanthrene unit of morphine leads to a series of potent analgesics. The best known example is etorphine (7,8-dihydro-7-(1-(R)-hydroxy-1-methylbutyl)-6,14-endo-ethenomorphine (2)) which is 8600 times the activity of morphine in guinea pigs after subcutaneous administration (1-3). Unfortunately, as the analgesic activity increases, the physical dependence liability and other side effects of the compound rise commensurately.

It has been generally accepted that the properly oriented piperidine ring and the properly situated phenolic nucleus are the most critical components to analgesic activity in the structure of morphine. The 4-phenylpiperidine system of morphine affords a tertiary amino group separated by 3 carbons (C-13, C-15 and C-16) from a hydrophobic aromatic nucleus. Almost all the strong narcotic analgesics which are used clinically have these structurally similar features (4,5).
Removing the ether bridge of morphine gives a series of potent analgesics called morphinans. The best known example is levorphanol (3-hydroxy-N-methylmorphinan (4)) which is used clinically in this country and is more potent and longer acting than morphine. Levorphanol and other morphinan derivatives have the main skeleton of the morphine structure, lacking only a hydrofuran ring and an allylic hydroxy system in ring C. Apparently, neither the hydrofuran ring, nor the olefinic alcohol system is necessary for the analgesic activity. The ring junctions in levorphanol are also identical to those in the natural morphine, C/D and C/B ring junctions being trans- and cis- fused respectively. The orientation of ring C is also not important in the analgesic activity. N-methylisomorphinan (3-hydroxy-N-methylisomorphinan (5)), an isomer of levorphanol with ring C and D being cis-fused, retains good analgesic activity (6). A free phenolic hydroxy group, however, is required for high analgesic potency.
in morphinan derivatives, as it is in morphine (7).

That ring C of morphine is not important for the analgesic activity can be realized from 6,7-benzomorphan derivatives. In this class of analgesics, the ring C of the morphinan structure is replaced by two alkyl substituents at positions now referred to as C-5 and C-9 of 6,7-benzomorphan (6). A simple example is 2'-hydroxy-2-methyl-5,9-dimethyl-6,7-benzomorphan (7,8). Isomers having 5,9-dimethyl substi-
tuents in a cis (β-isomer) or trans (α-isomer) relationship with respect to the piperidine ring have been isolated. A potent analgesic activity is found in both α(±) and β(±) racemates. In animals the α racemate is as active as morphine while the β racemate is even more potent. Like the situations in morphine and morphinan, the analgesic activity resides largely in the levo antipodes of α and β diastereoisomers (8). The α isomer is related sterically to morphine and morphinans and the β isomer to isomorphinan (5). In monkey it has been shown that complete dissociation of the undesired dependence liability from analgesia can be obtained in 6,7-benzomorphan derivatives. Unfortunately, this highly attractive property can not be observed in humans (9). Nevertheless, effective analgesics having less side effects than morphine have been obtained in the 6,7-benzomorphan series. Phenazocine (α-2'-hydroxy-2-phenethyl-5,9-dimethyl-6,7-benzomorphan (2), for example, is about three times as potent as morphine and causes less circulatory depression and other side effects. The development of tolerance is slower and the addiction liability is
less although the potential for the abuse still exists (10).

The hydroaromatic ring B in morphine, morphinan, and benzomorphan derivatives serves to lock the 4-phenylpiperidine system into a rigid unit so that the piperidine ring is constrained to a chair conformation and the phenyl ring to an axial orientation with the aromatic plane passing through C-2 and C-4 of the piperidine ring. This axial-phenyl-chair conformation of the 4-phenylpiperidine moiety, however, does not seem to be absolutely required for analgesic activity. Non-rigid cyclic derivatives in which the phenyl ring can not be constrained to an axial orientation retain the analgesic activity and the undesired toxicity of morphine. The best known examples are meperidine (10) and α-prodine (11). These two
simple piperidine derivatives possess an equatorial phenyl chair conformation. Meperidine has about one fifth the potency of morphine. In \( \alpha \)-prodine a propionoxy function replaces the ethoxycarbonyl group of 10 and results in potency rise. \( \alpha \)-Prodine, which is about two times as active as morphine, is one of the two racemic diastereoisomers of prodine. It has a trans 3-methyl/4-phenyl configuration and is about 3 times less active than the second form, \( \beta \)-prodine (12), which has a cis 3-methyl/4-phenyl configuration (11). In other potent prodine derivatives such as \( \alpha \)-promedol, the phenyl group resides

\[
\begin{align*}
\text{CH}_3\text{-N} & \quad \text{CH}_3 \\
& \quad \text{H} \\
& \quad \text{O}\text{C}\text{Et}
\end{align*}
\]

preferentially in the axial conformation (19).

Modification of the meperidine structure has generated a potent analgesic, fentanyl (13), in which the phenyl

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{-N} & \quad \text{N} \\
& \quad \text{O}\text{C}\text{Et} \\
& \quad \text{H} \\
& \quad \text{CH}_2\text{CH}_2\text{-N} \\
& \quad \text{O}\text{C}\text{Et}
\end{align*}
\]

and the acyl groups are separated from the piperidine ring
by a nitrogen atom. In man fentanyl is a powerful analgesic, about 100 times more potent than morphine (11).

Although the 4-phenylpiperidine moiety appears to be the most fundamental component of morphine, morphinan, benzomorphan, meperidine and their derivatives, the piperidine ring is not contained in the structures of a series of acyclic analgesics represented by methadone (14), diampromide (15), dextromoramide (16) and dextropropoxyphene (17). These
acyclic compounds are structurally related and possess good analgesic activity. The potency of diampromide approaches that of morphine in rats (12). Dextromoramide possesses a potency that a dose of 5 mg is equivalent to 10 mg of morphine for the treatment of post-operative pain (13). Dextropropoxyphene has been used extensively for the treatment of mild to moderate pain although its potency in man falls between aspirin and codeine (14). The potency of methadone is twice that of morphine and 10 times that of meperidine but its toxicity is 3 to 10 times greater than that of morphine (11). The $d$-methyl isomer of methadone, isomethadone (18), and the normethyl derivative, normethadone (19), are also effective analgesics although less potent than methadone (14). The carbonyl group of methadone has been converted to the alcohol and its acetyl ester. The alcohol derivative, methadol (20), is less potent while the acetyl derivative, acetylmethadol (21), is more potent and longer acting than methadone (15). Replacement of the propionyl group of methadone by hydrogen, hydroxy,
Acetoxy or propionoxy has resulted in a decrease or a lack of analgesic activity (11). It has been proposed that an electronic interaction between the amino nitrogen and the carbonyl carbon exists and locks the methadone molecule in a piperidine-like conformation (22) that may account for the analgesic activity (16, 17). The two phenyl groups in methadone are also important and removal of one of them causes a sharp decrease in analgesic potency (18). It is possible that second phenyl residue helps to maintain the propionyl group of methadone in
a position to simulate the alicyclic ring of morphine (11).

Replacement of the carbonyl group of methadone with a sulfonyl function has led to an analgesic sulfone. This sulfone analogue of methadone (23) is as active as methadone and carries the resemblance to the latter in that the analgesic activity mainly resides in the R-isomer. Like methadone, the R-isomer of the sulfone analogue possesses a potency 18 times that of the S-antipode (Table I). A preferred conformation similar to that of methadone was also proposed to account for the analgesic activity of 23 (16).

It has been widely accepted that narcotic analgesics interact with some specific receptors in the CNS to trigger the analgesic effects. A number of attempts have been made to localize the sites of action of narcotic analgesics within the CNS. The techniques that have been employed involve microinjection of narcotic agonists or antagonists into various brain areas, and observation of the inhibition of nociceptive reactions of agonists or examination of the action of antagonists...
Table I

Analgesic activities of methadone and its sulfone analogue in mice (19)

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<thead>
<tr>
<th>Isomer</th>
<th>Configuration</th>
<th>Activity a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>+</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>S</td>
</tr>
<tr>
<td>Sulfone analogue of methadone (23)</td>
<td>+</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>S</td>
</tr>
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a (±)-methadone = 100
against the effects of systemic administration of agonists. Studies of precipitation of the withdrawal syndrome in morphine-dependent animals or autoradiographic studies of the distribution of radioactive analgesics in the CNS have also been employed. The sites of action of opiates have been found to occur with very considerable regional variations, and the results presented from different laboratories are not in agreement. The localization of these central sites has been ascribed to the anterior thalamus (20), posterior hypothalamus (21), periventricular-periaqueductal region of midbrain (22, 23), and the area surrounding the third ventricle (24). Reports from a group represented by Herz and Teschemacher, however, have presented disparate results. They showed that the structures easily reached from the 4th ventricle (medulla, pons and lower part of midbrain) were the main sites of action of analgesics (25-27). The discrepancies in the central localization of opiate receptors obviously needs to be resolved. Unfortunately, the in vitro binding studies with narcotic agonists or antagonists have not provided an unambiguous answer. Regional study of stereospecific binding of $^3$H-naloxone to brain homogenate obtained from different areas of rat brain revealed that the greatest amount of stereospecific binding was found in the corpus striatum. The midbrain and the brain stem exhibited only one-quarter and one-eighth respectively as much stereospecific binding (28). This pattern of stereospecific binding was also generally observed in monkey and human brains by using $^3$H-dihydromorphine (29). The greatest amount
of stereospecific binding was observed in amygdala, periaque-
ductal area of midbrain, hypothalamus, thalamus and caudate
nucleus. The binding was found to be very low in the area
surrounding the 4th ventricle, in contrast to the results of
Hertz et al. (25-27). On the other hand, Goldstein and his
coworkers (30) demonstrated a set of stereospecific binding of
$^3H$-levorphanol in mice which occurred predominantly in the
brain stem, especially in medulla-pons area. This set of
stereospecific binding was shown to possess properties differ-
ent from those of naloxone binding (28). It was argued that
two groups of workers were dealing with different sets of
opiate binding receptors which were related but different
somewhat in structure and function (30). The situation can not
be clarified until the various opiate receptors are separated
and studied individually. Nevertheless, there has been a common
finding in that the opiate receptor bindings are associated
with neuronal membranes, mainly with microsomal and crude
mitochondrial fractions (28, 29, 30-32). An $^3H$-etorphine-
macromolecule complex has been recently isolated when the
membrane fraction prepared from rat brain homogenate was treat-
ed with $^3H$-etorphine. It was shown that this isolated bound
macromolecule may represent the pharmacological receptor (33).

The existence of opiate receptors has been supported
by the recent isolation of some endogenous substances with
opiate activities (34-39). Hughes (40, 41) identified a sub-
stance in the brains of pigs, cows, guinea pigs, rats, rabbits
and mice, that mimicked the effect of morphine to inhibit con-
tractions of guinea pig ileum. This substance which is called enkephalin and has a molecular weight of 1000 was found to be a mixture of two closely related pentapeptides having the following sequence:

Tyr-Gly-Gly-Phe-Met (Methionine-Enkephalin)
Tyr-Gly-Gly-Phe-Leu (Leucine-Enkephalin)

Similar peptides were also isolated by Snyder and Ternius (34, 35, 39, 42, 43). Goldstein identified another peptide from pituitary gland, having a molecular weight of 1800. He thought that this peptide may be the precursor of enkephalin (44, 45). It is interesting to note that enkephalin has a tyramine moiety (tyrosine minus COOH group) in the terminal portion, which is a common feature of many opiate agonists and antagonists (46, 47). The conformation of met-enkephalin has been proposed on the basis of structural similarities with morphine and related analgesics (64-67).

Opiate receptors are also located in the peripheral nervous tissues of certain animal species. The transmission from the myenteric plexus to the longitudinal muscle is depressed by morphine in guinea pigs (48, 49). The transmission from vagal nerve to sinoatrial node is morphine sensitive in rats and rabbits (50). As far as adrenergic autonomic junctions are concerned, the nictiating membrane of cats and the vas deferens of mice are morphine sensitive (24, 51-53).

The depressant actions of narcotic analgesics on the guinea pig ileum have been intensively investigated in recent years (28, 48, 49, 54-62). Morphine and other potent narcotics
stereospecifically produce depressant effects on the electrically evoked contractions of guinea pig ileum in the concentration range of $10^{-8}$ to $10^{-9}$ M (49). The potencies of narcotic agonists and antagonists in the inhibition of contractions have been demonstrated to predict accurately the analgesic potencies of these drugs in animals and in man (63). Tolerance to actions of narcotic analgesics and withdrawal excitations precipitated by using narcotic antagonists such as naloxone have also been demonstrated in this tissue (49, 61). It has now been widely accepted that guinea pig ileum is a reliable model for analgesic studies. Its uses in the investigation of narcotic analgesics have certain advantages. Effects of absorption, distribution, biotransformation and excretion of the drugs are limited or almost completely excluded. In the studies of structure-activity relationship of narcotic analgesics in whole animals, serious difficulties in the interpretation of results have arisen due to the considerable variation in the lipophilicity of narcotic analgesic drugs and therefore in their ability to penetrate the blood brain barrier. It has been known that, in whole animals, relatively hydrophilic narcotics such as morphine are more active after intraventricular than intravenous administration, while no significant difference is found for more lipophilic compounds (26, 68, 69).

The nature of opiate receptors has been demonstrated to be protein (33, 70), phospholipid (71, 72) and proteolipid (73, 74). It is likely that the opiate receptors are membrane bound complexes whose stereospecific binding is dependent on
the integrity of both proteins and phospholipids (73). The shape of the opiate receptor has been proposed by Beckett and Casy (17) according to the common structural features of narcotic analgesics and studies of structure-activity relationships on these drugs. A receptor surface was formulated and later modified (19) to accommodate the rigid skeleton of natural morphine and other cyclic and acyclic analgesics (Figure I). The receptor was proposed to consist of three essential sites: a flat surface which allows binding with the phenolic or aromatic nucleus of the analgesic molecule, an anionic site...
which associates with the positively charged ammonium group of the drug molecule, and a cavity which accommodates the projecting C(15)-C(16) portion of piperidine ring in morphine and other analgesic molecules. The stereochemical requirements for the analgesic activities of morphine, morphinan, 6,7-benzomorphan and their derivatives have been attributed to the spacial constraint of the binding sites on the rigid receptor surface. In the explanation of analgesic activities of certain acyclic compounds such as methadone, methadol, acetylmethadol and diampromide etc., Portoghese has postulated that more than one binding mode can occur in the interaction of these flexible drugs with the same analgesic receptor (75, 76).

Recently, the opiate receptor has been proposed (5) to exist in two interconvertible states which are responsible for triggering the agonistic and antagonistic activity respectively. Sodium ion is thought to modulate the interconversion of the two states by acting on the allosteric site of the receptor. Under the prevailing sodium concentration in the brain, the opiate receptor is considered to exist predominantly in the antagonistic state.

As mentioned previously, the analgesic activity of methadone was attributed to the piperidine-like conformation resulting from an intramolecular interaction between the nitrogen atom and the carbonyl carbon (16). This electronic interaction appears to be present in the crystal structure of methadone free base. A short distance of 2.91 Å between the two atoms was observed by Bye (77). In solution, the magnitude
of this interaction is considerably weaker than what is generally believed. Studies by circular dichroism and proton magnetic resonance (78) indicated that N...CO interaction of methadone is likely present in the molecule so that in CDCl₃ solution three possible conformers, 14a, 14b and 14c were present in approximately 1:1:2 ratio. The N...CO internal association is possible in the conformers 14a and 14c, but it certainly did not predominate to the exclusion of the unassociated rotamer 14b. In CD₃OD solution a conformeric distribution of approximately 1:4:5 (14a:14b:14c) occurred. The per-
sistence of 14b in both solvents is surprising in light of considerable steric interactions. Its presence was explained by the solvation effect of polar solvents, which tend to diminish the magnitude of intramolecular association (78). In a more recent study of 5-methylmethadone it is believed that one of the pharmacophoric conformations of diphenylpropylamine analgesics possesses an antiperiplanar-like disposition of the Ph₂C(=O)Et and N(CH₃)₂ as represented by 14b (79).

At physiological pH, methadone appears as the protonated form, which is expected to be the species that interacts with the narcotic receptor. According to Beckett and Casey, an electronic attraction between the positive ammonium group and the carbonyl oxygen is still possible and the piperidine-like conformation that fits the hypothetical receptor still exists (16). This electronic interaction, however, was not observed in the crystalline structure of methadone hydrobromide which was found to exist in an antiperiplanar conformation (80).
Antiperiplanar conformation of methadone hydrobromide

Measurements by using circular dichroism and proton magnetic resonance methods also indicated that the presence of such an extended form could not be excluded (78). A preferred antiperiplanar conformation was also observed for isomethadone (18) and normethadone (19) in organic solutions (78, 81).

Although methadone may exist in certain preferred conformations in physiological fluid, whether or not such preferred conformations can be related to the analgesic activities of methadone is questionable. It has been now fairly well accepted that both the receptor macromolecule and the
drug molecule can influence the conformation of each other. The preferred conformation of methadone may be perturbed by the interaction forces existing between the drug and the receptor. Thus the preferred conformation of methadone in solution may not be the pharmacological conformation, the conformation that fits the perturbed receptor macromolecule. To investigate the nature of interaction between the analgesic receptor and the structurally flexible methadone molecule, conformationally restricted analogues of methadone seems to be better suited. A few conformationally rigid methadone analogues, such as 24 and 25 have been studied. In general, such structural modifications of methadone resulted in less active or inactive compounds (82). It is possible that the stereochemistry of these rigid analogues of methadone does not satisfy the requirements demanded by the opiate receptor.

Thietane 1,1-dioxides such as 26 are considered to be structurally similar to the sulfone analogue of methadone
which is believed, as mentioned in page 11, to interact with opiate receptor in the same manner as that of 22.

Studies of these relatively new and less investigated cyclic sulfones may lead to development of new potent diphenylpropylamine type analgesics containing a significant degree of conformational rigidity.

The present project continues previous investigations, in our laboratory, of thietane 1,1-dioxides for medical uses (83-86). Because of the synthetic difficulty encountered in the synthesis of 26, Coates and Haya (84, 85), on the basis of certain assumptions and proposals, synthesized 2,4-diphenyl-3-dimethylaminomethylthietane 1,1-dioxides (27-29) and 2-phenyl-3-dimethylaminomethylthietane 1,1-dioxides (30, 31) as an approach to apply the semirigid thietanes to the studies of methadone-receptor interaction. All these compounds were found to be devoid of analgesic activity. In comparison with the structure of 26, 27-31 lacks a phenyl group on C(2). It is possible that this missing phenyl group, rather than the one already placed on
the C(2) carbon of thietane ring, has the required orientation to bind with the flat surface of the analgesic receptor (Figure I). It was considered, therefore, that synthesis of compounds 32-36, with two phenyl groups on the C(2) carbon, would be of interest. The high similarity of these compounds to the sulfone analogue of methadone (23) reasonably suggested that they would be potent analgesics. The synthesis of 35 and 36 was desirable to explore the suggestion by previous workers.
that a close approximation of amino side chain to sulfone group may be necessary for the achievement of analgesically active thietane derivatives.
Two review articles on thietane chemistry have appeared in the literature (87, 88). Surveys on the same subject including the literature to 1973 are found in two dissertations (84, 85). The material presented in this section is a brief summary of publications that have not been previously covered, with emphasis on the chemistry relevant to the research problem of the present project.

Thietane derivatives have been known to possess non-planar structures. The ring puckering vibration of the thietane ring was observed in ir (89), far ir (90), and pmr (91) spectra. The determination of molecular structure of thietane (37) by electron diffraction, showed that the bond lengths of C-S, C-C, and C-H were 1.84, 1.55 and 1.10 Å respectively and that the bond angles of C-S-C and H-C-H were 76.8 and 112° respectively. The angle of puckering defined by C2-S-C4 plane and C2-C3-C4 plane was 26° (92). In substituted thietanes, the non-bonded interactions of the substituents would particularly favour a puckered structure. Infrared studies showed that 3-chlorothietane possessed a bent ring with the chlorine atom being equatorial (93). The x-ray crystallography showed that
L-(p-chlorobenzenesulfonamido)-\(\beta\)-propiothiolactone was puckered by about 13° (94). Puckering of the ring has also been observed in the thietane 1-oxide derivatives. The crystal structure of cis-2,4-diphenylthietane trans-1-oxide (38), determined by x-ray crystallography, possessed a puckered thietane ring to accommodate two equatorial phenyl groups. The bond distances and the bond angles were similar to those of unsubstituted thietane, the bond lengths of S-C and C-C being 1.85

and 1.57 Å respectively; and the bond angles of C-S-C, S-C-C and C-C-C being 76.5, 86.9 and 93.9° respectively (95). The angle of puckering was found to be 41.9°. The sulfinyl oxygen was shown to have equatorial orientation (95). The equatorial orientation of sulfinyl oxygen was also observed in both cis- and trans-3-(p-bromophenyl)thietane 1-oxide (96). Thietane 1,1-dioxide derivatives also possess a nonplanar thietane ring. Ziegler et al. studied the molecular structure of 2,2-dimethylthietane 1,1-dioxide (39) by x-ray methods. They showed that the thietane ring was puckered by 23° (97). Andretti et al. reported that the thietane ring of cis-2-chloro-3-mor-
Pholino-4,4-dimethylthietane 1,1-dioxide was puckered by 26.6° (98).

The x-ray studies of cis-2,2-diphenyl-3,4-dichlorothietane and its oxidation product, cis-2,2-diphenyl-3,4-dichlorothietane 1,1-dioxide showed an interesting result (99, 100). The thietane rings in both compounds were puckered, by angles of 29 and 31.3° respectively. The conformations of C-Cl bonds were 3-equatorial and 4-axial with respect to the thietane ring in the former compound (40). The oxidation of thietane 40 to sulfone 41 resulted in 3-axial and 4-equatorial conformations of two C-Cl bonds in the thietane 1,1-dioxide.
The ring puckering and the preferred axial orientation of the 3-substituents were also reported by Cistaro et al. in their pmr study of 3-substituted thietane 1,1-dioxides (101).

Thietanes are reactive compounds probably because of the high strain of the four-membered ring and the availability of nonbonded electrons on sulfur. In the presence of acid, thietanes readily undergo polymerization. Ring cleavage reactions take place when thietanes are treated with base or electrophilic reagents. The electrophilic reagents such as methyl iodide probably form a sulfonium salt with thietane leading to the ring opening (87, 88).

\[
\text{S} + \text{NH}_3 \rightarrow \text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{SH}
\]

Thietanes can be readily oxidized to sulfoxides or sulfones. Unlike the thietanes, the oxidized analogues are more stable and usually appear as crystalline products. Thie-

\[
\text{S} \rightarrow \text{SO} \rightarrow \text{SO}_2
\]
tane 1,1-dioxides are thus frequently prepared as derivatives of thietanes for easy handling. Certain thietanes which cannot be obtained directly have been obtained by reduction of the corresponding thietane 1,1-dioxides with lithium aluminum hydride.

\[ \text{SO}_2 \quad \text{LiAlH}_4 \quad \text{S} \]

An efficient route to thietane 1,1-dioxides is the cycloaddition of strongly nucleophilic olefins (e.g. enamines, ynamines, vinyl ethers, ketene acetals and ketene aminals) with an appropriate sulfene generated \textit{in situ} by the reaction of sulfonyl chloride and triethylamine. These cycloaddition reactions have been extensively reviewed (84, 85, 102-107). A brief summary is presented here.

The sulfonyl chlorides used in the cycloaddition reactions are unsubstituted or substituted \textit{methanesulfonyl} chlorides. With \textit{methanesulfonyl} chloride, the cycloaddition reaction results in formation of 3-substituted or 2,3-substituted thietane 1,1-dioxide. Treating \textit{methanesulfonyl} chloride
(42) with substituted N-methyl-N-phenylvinylamines (43), for example, was reported to generate 2,3-substituted thietane 1,1-dioxides (44) (108). With substituted methanesulfonyl chlorides the cycloaddition leads to the formation of 2,3- or 2,3,4-substituted thietane 1,1-dioxides. The reaction of morpholino enamines (45) with substituted 2-halomethanesulfonyl chlorides leads to the formation of 2,3- or 2,3,4-substituted thietane 1,1-dioxides.
chlorides (46), in the presence of triethylamine, was reported
to give substituted 2-halo-3-morpholinothietane 1,1-dioxides
as a mixture of cis and trans isomers (47, 48) (109). The be-
havior of these thietane 1,1-dioxide products towards the
treatment of base was studied (110). The ring substituents and
their stereochemistry were shown to determine the reaction
paths. The 4,4-dimethyl derivatives (49, 50) underwent halogen
halide elimination to give a thiete 1,1-dioxide 51 upon treat-
ing with aqueous alcoholic NaOH. It was proposed that trans

\[ \text{\( X = \text{Cl, Br, I} \)} \]

hydrogen halide elimination was the main process and that pre-
isomerization of the trans isomer to the cis form occurred be-
fore the dehalogenation. In the case of 2,4,4-trimethyl-3-mor-
pholinothietane 1,1-dioxide (52), the cis isomer was readily dehalogenated to give 53 while the trans isomer was unreactive towards the base probably because the isomerization was not possible in the trans isomer. In those derivatives bearing the 3,3-disubstituents (54), the hydrogen halide elimination was structurally prevented. Ring cleavage was the preferred reaction leading to formation of 5-phenyl-2H-1,3-oxathiole 3,3-dioxide (56) and other acyclic fragments through an enamine intermediate (55). Upon refluxing an ethanolic solution of
cis- or trans-2-chloro-3-morpholino-3-phenyl-4-methylthietane 1,1-dioxide (54, \( R=\text{CH}_3 \)), the sulfonylenamine (55, \( R=\text{CH}_3 \)) formed underwent intermolecular rearrangement to give 3-(2-(2-chloroethoxy)ethyl)-5-methyl-4-phenyl-\( \Delta^4 \)-thiazoline 1,1-dioxide (58) via the formation of a quaternary ammonium intermediate (57) (111).

The cycloaddition of an enamine intermediate with sulfene was proposed by Chen and Chow (112) for the formation
of substituted thietane 1,1-dioxides (61) in the reaction of \( \alpha \)-aminoketoximes (59) with phenylmethanesulfonyl chloride (60) in the presence of pyridine. The amino group of the ketoxime (59) was strategically placed at a position to facilitate ring cleavage. The possible enamine intermediate (62) was formed and reacted with phenylsulfene. It was proposed that the bulky groups (phenyl, piperidino and alkyl), during the cycloaddition process, staggered themselves around the ring to
avoid undue steric crowding, so that all the substituents on the thietane ring assumed a trans relationship.

It is not known whether the cycloaddition of sulfenes with enamines is a concerted process (path 1) or a two-step reaction involving formation of zwitterion (63) (path 2). A two-step addition process has been chosen by various workers in explaining the nature of product formation (103, 112-117).
In a study of cycloaddition reactions of a number of N,N-di-substituted 2-methyl-1-propenylamines (64) with substituted methanesulfonyl chlorides (65), Truce et al. (118) reported that the reactions led to a mixture of cis and trans substituted thietane 1,1-dioxides (66, 67). The cis products in which the amino moiety and the sulfene substituent $R^1$ assume a less thermodynamically stable cis relationship, were found to be predominant in many reactions particularly when the sul-
fenes used were derived from methanesulfonyl chloride containing an \( \text{\textalpha}\)-phenyl, \( \text{\textalpha}\)-halo or \( \text{\textalpha}\)-tolyl substituent, or from ethanesulfonyl chloride bearing an \( \text{\textalpha}\)-chloro, or \( \text{\textalpha}\)-cyano moiety. The steric factors appeared not to determine the stereoselectivity in the formation of \textit{cis} products. A rationale for this observed stereoselectivity was postulated on the basis that the reaction was a two-step process and proceeded via the formation of a zwitterion intermediate. The electrostatic attraction between the positive and the negative charges of the dipolar zwitterion intermediate (68), which can be delocalized by the amino and
the phenyl moieties respectively was suggested to favour the cis geometry of products. This explanation was supported by the data that cis preference was not observed for products derived from the sulfenes bearing substituents without appreciably negative character.

The cycloaddition of vinylsulfene (69) with morpholino or piperidino enamine (70) was reported (119) to proceed with no stereoselectivity, giving a 1:1 mixture of cis and trans thietane 1,1-dioxide products (71, 72). Whether the post-isomerization of the cis isomer to the trans form occurred was not known. It was reported that 71 isomerized to 72 when the former was treated with butyl lithium.
Thietane 1,1-dioxides are not the only type of products formed in the reaction of sulfenes with enamines. In certain conditions, sulfenes react with enamines to form acyclic substitution products. The reaction of phenyl sulfonyl chloride (60) with 1-pyrrolidinocyclohexene (73) was reported to give an acyclic sulfone 74 (120). Reaction of sulfonyl chloride 75 with enamine 76 in the presence of triethylamine afforded acyclic product 77 in 86% yield (121). In the reaction of enamine 78 with cyanomethanesulfonyl chloride (79) an acyclic intermediate 80 was also proposed to account for the isolation of benzoylmethyl cyanomethyl sulfone (81) (85). Certain α-cyanothietanes 1,1-dioxides (82) (122) can be
generated by this method depending on the electronic nature and the bulkiness of the ring substituents. The reaction of 79 with enamine 83 gave only acyclic product 85. It was pointed out that thietane 84 may be formed before rearrangement to 85 (117). In certain reactions the formation of acyclic substitu-
tion products may be attributed to the steric and electronic factors that were unfavorable for the intermolecular cyclization of the zwitterion intermediate 63 and thus allowed for the formation of acyclic products as an alternate route.

Although certain thietanes can be efficiently prepared by reducing the corresponding thietane 1,1-dioxides, in the situations where the synthesis of thietane 1,1-dioxide by cycloaddition is not possible or thietane 1,1-dioxide is decomposed by the reducing conditions employed, direct synthesis of thietane may be an alternate approach. The classic method of synthesis of thietanes involves the generation of a thiolate anion containing a good leaving group separated by three carbons from the sulfur atom. Intramolecular cyclization of this thiolate anion results in formation of 2-substituted or
3-substituted thietanes. Synthesis of 2-substituted thietanes by this method generally results in low yields probably due to the steric hindrance of the cyclization process by the substituents (122).

\[ \text{C-C-C-R} \rightarrow \text{S} \]

\[ R = \text{OCN, halogen, O-S-\text{-CH}}_3 \text{ etc.} \]

Dubs et al. (123) reported a method to prepare a series of substituted 2-thietanols 87 in 16-84% yields by treating \( \alpha, \beta \)-unsaturated aldehydes 86 with hydrogen sulfide in the presence of triethylamine. It was assumed that the thiolate ion was formed and underwent intramolecular cyclization.

\[ \begin{align*}
R^1 \text{-C-C-C-CHO} + H_2S & \xrightarrow{\text{Et}_3N} R^1 \text{-S-CH} \text{-OH} \\
R^1 = \text{H, CH}_3, \text{CH(CH}_3)_2, \text{Et} & \\
R^2 = \text{H or CH}_3
\end{align*} \]
to give the products.

Mayer (124) developed a method of synthesis of 2,2-dimethylthietane (89). He treated 1,3-dichloro-3-methylbutane (88) with hydrogen sulfide in the presence of a catalytic amount of aluminum chloride and isolated 2,2-dimethylthietane (89) in 90% yield. It was proposed that the reaction proceeded via the formation of intermediate 90 or 91. The aluminum chloride might activate the double bond to facilitate the attack of hydrogen sulfide.
Capanovich et al. discovered a method of cyclizing the bromomethylthioester 92 to 3,3-diphenylthietan-2-one (94). The carbanion 93 was probably the intermediate of the cyclization process (125).

\[
\begin{align*}
\text{CH-C-S-CH}_2\text{Br} & \quad \overset{\text{Et}_2\text{N}}{\rightarrow} \quad \text{[structure]} \quad \overset{\text{[structure]}}{\rightarrow} \quad \text{CH-C-S-CH}_2\text{Br} \\
\end{align*}
\]

A relatively new and very useful method of preparing thietanes is the photocycloaddition of thiocarbonyl compounds with olefins bearing a variety of substituents. This method has led to the synthesis of many substituted thietanes which cannot be generated by the classical intramolecular cyclization of thiolate or cycloaddition of sulfenes with olefins. The formation of thietane intermediates upon irradiating a mixture of thiobenzophenone and olefins was first proposed by Kaiser and Wulfers (126). The isolation of thietanes was subsequently demonstrated by the Japanese photochemists in 1969; Ohno et al. showed that irradiating a mixture of thiobenzophenone (95) and certain olefins (96), with 366 nm light or 589 nm light, generated thietanes (97) in good yields (127-129). The cycloaddition reaction was found to be stereospecific. The photocycloaddition of cis- and trans- dichloroethylene (96, \(R^1=R^2=\text{Cl}\)), for example, gave exclusively cis-3,4-dichloro-2,2-
\[
\text{R}^1 = \text{Cl, CH}_3\text{COO, CH}_3\text{COO, CN}
\]
\[
\text{R}^2 = \text{H, Cl, CH}_3
\]
diphenylthietane (\text{97, } \text{R}^1=\text{R}^2=\text{Cl}) and trans-3,4-dichloro-2,2-diphenylthietane (\text{97, } \text{R}^1=\text{R}^2=\text{Cl}) respectively. In addition to the generation of thietanes (1:1 thiobenzophenone/olefin adducts), the formation of 1,3- or 1,4- dithianes (2:1 thiobenzophenone/olefin adducts) has also been observed in some photocycloaddition of thiobenzophenone with olefins. The photochemical reaction of thiobenzophenone with styrene (\text{98}), for example, afforded both 1,4-dithiane \text{99} and thietane \text{100} with yields depending on the concentrations of \text{95} and \text{98} (127).
On the basis of the results obtained from reactions of thiobenzophenone and olefins bearing various substituents, Ohno and his coworkers (127-129) concluded that olefins bearing electron-withdrawing groups (e.g. CN, COOCH₃, Cl, OCOCH₃ etc.) upon reacting with thiobenzophenone excited by 366 nm light gave thietanes, and that olefins bearing electron-releasing substituents (e.g. alkyl, alkoxy, phenyl etc.) upon reacting with thiobenzophenone excited by 366 or 589 nm light, generated thietanes or dithianes depending on the nature of the olefins. The factors that governed the course of photocycloaddition reactions appeared to be both steric and electronic. The reactive species in the reactions was suggested to be the light-excited thiobenzophenone since the olefins used in the photochemical reactions were transparent in the wavelength regions employed (127, 132). The irradiation was proposed to cause two types of electronic transition of thiobenzophenone, depending on the wavelength of light used (127). The irradiation at long wavelength (589 nm) produced transition of an electron from non-bonding orbital (n) to pi-antibonding orbital (\( \pi^* \)) of the thiocarbonyl group of thiobenzophenone. The resulting excited state (n→\( \pi^* \)) possessed an energy 40-43 Kcal higher than the ground state of thiobenzophenone and has been suggested to be a triplet, the spin of the excited electron in the \( \pi^* \) orbital being unpaired with that of the unexcited electron in the n orbital. The irradiation at short wavelength (366 nm) induced transition of an electron from pi-orbital (\( \pi \)) to pi-antibonding orbital. The resulting excited state (\( \pi \to \pi^* \)) oc-
cupied an energy level about 50 Kcal higher than the n→π* state and has been suggested to be a singlet, two electrons in each orbital being paired (127, 130, 131). Ohno et al. suggested that the n→π* triplet state of thiobenzophenone behaved like a thyl radical while the π→π* singlet state behaved like a thiolate anion (RS−). Two kinds of mechanism were thus postulated for the photochemical reactions of thiobenzophenone with olefins (127). With electron deficient olefins, the π→π* species of thiobenzophenone formed a charge-transfer complex leading to the formation of thietanes. The energy of n→π* species of thiobenzophenone was considered to be too low to transfer to the olefins. However, with electron rich olefins, the n→π* species of thiobenzophenone reacted through a diradical mechanism. The sulfur atom of thiobenzophenone attacked the olefin leading to the formation of diradical 101 which either intramolecularly cyclized to form thietane or reacted with a second molecule of thiobenzophenone resulting in generation of 1,3- or 1,4- di-thiane (102, 103). The factors that determined the reaction

\[
\begin{align*}
\text{S} & \quad \rightarrow \quad \text{C} \\
\pi & \quad \rightarrow \quad \pi^* \\
\text{366 nm} & \\
\begin{array}{c}
\text{S} \\
\text{C} \\
\text{C}
\end{array} & \quad \rightarrow \\
\begin{array}{c}
\text{C} \\
\text{S}
\end{array} & \quad \rightarrow \\
\begin{array}{c}
\text{C} \\
\text{C}
\end{array} & \quad \rightarrow \\
\begin{array}{c}
\text{S}
\end{array}
\end{align*}
\]
path were suggested to be the concentration of thiobenzophenone and the steric environment of the diradical.

\[
\begin{align*}
&\text{\chem{\begin{array}{c}
\text{S} \\
\text{C} \\
\text{C} \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\xrightarrow{\text{n} \to \pi^* \ 589 \text{ nm}} \\
&\text{\chem{\begin{array}{c}
\text{S} \\
\text{C} \\
\text{C} \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\xrightarrow{\text{C=C<}} \\
&\text{\chem{\begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\text{\chem{\begin{array}{c}
\text{S} \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\text{or} \\
&\text{\chem{\begin{array}{c}
\text{S} \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\xrightarrow{\text{102}} \\
&\text{\chem{\begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\text{\chem{\begin{array}{c}
\text{S} \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\text{\chem{\begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\text{\chem{\begin{array}{c}
\text{S} \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5
\end{array}}} \\
&\xrightarrow{\text{103}}
\end{align*}
\]

The early work on the photocycloaddition of thio-
benzophenone with olefins has been reviewed (130, 132). Recent studies of the photocycloaddition reactions using various substituted olefins have led to the generation of many new substituted thietanes. A summary of these new findings is presented in the remainder of this section.

When a mixture of a thione (105, 107) and a pentadiene (104, 109) was irradiated under 589 nm light ($n \rightarrow \pi^*$ band), the corresponding thietane (106, 108, 110, 111) was isolated (133). An acyclic rearranged adduct (112) was also isolated in the reactions of 104 with 105.

\[
\begin{align*}
\text{CH}_3\text{C} & = \text{C} \text{CH}_3 + \text{S} \overset{hv}{\rightarrow} \text{CH}_3\text{R} \overset{\text{R-C-R}}{\text{S}} \\
& \text{R} = \text{C}_6\text{H}_{11} \quad \text{or} \quad \text{C}_6\text{H}_{10}\text{CH}_3 \\
& \text{104} \quad \text{105} \quad \text{106}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{C} & = \text{C} \text{CH}_3 + \text{S} \overset{hv}{\rightarrow} \\
& \text{104} \quad \text{107} \quad \text{108}
\end{align*}
\]
The photocycloaddition of methoxyallene (113) with thiobenzophenone (95) at 589 nm was reported to give thietane 114 together with a benzothiane 115. It was assumed that the n→π* triplet thiobenzophenone attacked methoxyallene at the central carbon atom resulting in formation of a biradical which then cyclized to yield thietane and benzothiane. With xanthene-9-thione (107) the photocycloaddition of methoxyallene (113) gave only thietane 116. No ben-
zothiane was detected (134a).

\[
\begin{align*}
&\text{H}_2\text{C} = \text{C} = \text{C} \text{H} + \text{C} = \text{C} \text{S} \text{C} \text{C}_{\text{aryl}} \\
&\quad \xrightarrow{\text{hv}} 113 + 95
\end{align*}
\]

\[
\begin{align*}
&\text{CH}_3\text{O} \text{H}_2\text{C} = \text{C} \text{S} \text{H}_2\text{C} = \text{C} \text{H} + \text{C} = \text{C} \text{S} \text{C} \text{C}_{\text{aryl}} \text{CH}_2\text{OCH}_3 \\
&\quad \xrightarrow{\text{hv}} 114 + 115
\end{align*}
\]

\[
\begin{align*}
&\text{H}_2\text{C} = \text{C} = \text{C} \text{H} + \text{C} = \text{C} \text{S} \text{C} \text{C}_{\text{aryl}}^{\pi^*} \\
&\quad \xrightarrow{\text{hv}} \text{CH}_3\text{O} \text{H}_2\text{C} = \text{C} \text{S} \text{H}_2\text{C} = \text{C} \text{H} + \text{C} = \text{C} \text{S} \text{C} \text{C}_{\text{aryl}} \text{CH}_2\text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
&\text{H}_2\text{C} = \text{C} = \text{C} \text{H} + \text{C} = \text{C} \text{S} \text{C} \text{C}_{\text{aryl}}^{\pi^*} \\
&\quad \xrightarrow{\text{hv}} 114 + 115
\end{align*}
\]
Gotthardt and Listle (135), by irradiating mixtures of thiocarbonates (117, 123) and substituted olefins (118-121) with n→π* band light (328 nm), isolated the corresponding thietanes (122, 124). When they irradiated mix-
tures of thiophosgene (125) and olefins (118-120), the expected thietane products (126) were also obtained (136).

\[
\begin{align*}
\text{S} & \quad \text{Cl-C-Cl} & + & \quad \text{R}^1 \quad \text{C}=\text{C} \quad \text{R}^2 \quad \text{R}^3 \\
\text{Cl-C-Cl} & \quad \text{CH}_3 \quad \text{CH}_3 & \quad \text{hv} & \quad \text{455 nm} \\
& & & \quad \text{CH}_3 \quad \text{Cl}
\end{align*}
\]

125 \quad 118-120 \quad 126

With olefins 119 and 120 the photocycloaddition of thiophosgene also generated acyclic adducts 127 and 128 respectively. The 2,2-dichlorothietanes (126) isolated rapidly underwent dechlorination, upon chromatography on silica gel, to give the corresponding thietanones (129-131). It

\[
\begin{align*}
\text{Cl} & \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \\
\text{CH}_3 & \quad \text{CH}_3 \quad \text{S} \quad \text{C}=\text{C} \quad \text{CH}_2 \\
\text{Cl} & \quad \text{CH}_3 \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3
\end{align*}
\]

127: \( \text{R}^1=\text{R}^2=\text{CH}_3; \text{R}^3=\text{H} \)
128: \( \text{R}^1=\text{CH}_3; \text{R}^2=\text{R}^3=\text{C(CH}_3)_2 \)
was suggested that the reactive thiophosgene was the n→π* triplet species.

The photocycloaddition of O-methyl or O-ethyl thiobenzoate (132) with substituted olefins (133, substituents are H, benzyl, methyl, ethyl, propyl) afforded 2-

![Chemical structure](image)

phenyl-2-alkoxythietane derivatives (134). The reaction was attributed to the formation of n→π* triplet species of thiobenzoate (137).

When a mixture of diarylthioketone (135) and vinyl ethyl ether (136) was irradiated under 589 nm light, the reaction resulted in the formation of thietane (138) or dithiane (139) depending on the concentration of thioketone used (135). A biradical intermediate was suggested for the product formation. At a low concentration of thioketone, the biradical intermediate (137) underwent intramolecular cyclization to form the thietane 138. At a high concentration of thioketone, the biradical intermediate (137) was trapped by a second molecule of thioketone leading to the formation of dithiane 139. The photocycloaddi-
tion of thioketone with electron-deficient olefins led to more interesting results (135). With methyl acrylate (140), the reaction of π→π* species of thiobenzophenone resulted in the formation of thietane 141 and the reaction of n→π* species of thiobenzophenone afforded a 2:3 mixture of thietane 141 and benzothiane 142. Apparently the formation of thietane 141 was not governed by the wavelength used. It was observed that the benzothiane 142 was generated thermally by heating a mixture of thiobenzophenone and methyl acrylate at 40-50°. The photocycloaddition of thione 143 with acrylonitrile (144) or methyl acrylate (140) at 589 nm
yielded thietane 145. This again showed that the $\pi \rightarrow \pi^*$ excitation of the thiocarbonyl compounds was not necessary for thietane formation from electron deficient olefins, in contrast to the result reported by Ohno and his coworkers (138). The photocycloaddition of xanthione with methyl acrylate also supported the argument. Irradiating a mix-
ture of xanthene-9-thione (107) and methyl acrylate (140) at either 589 nm (n→π* excitation) or 405-408 nm (π→π* excitation) resulted in the formation of spirothietane 146.

\[
\begin{align*}
\text{107} & \quad + \quad \text{CH}_2=\text{CHCOOCH}_3 \\
\text{140} & \quad \xrightarrow{n \rightarrow \pi^*} \quad \text{or} \quad \pi \rightarrow \pi^* \\
\text{146} & 
\end{align*}
\]

The photocycloaddition of nitrogenous thiocarbon-yl compounds with olefin was reported by Fourrey et al. (139). The expected spirothietanes 149 and 151 were obtained when a solution of 4-thiouracil derivatives (147, 150) and methacrylonitrile (148) was irradiated.

\[
\begin{align*}
\text{147} & \quad + \quad \text{H}_2\text{C}=\text{C}<\text{CH}_3 \\
\text{148} & \quad \xrightarrow{\text{hv}} \quad \text{149} \\
\text{R} & = \text{H or CH}_3 \\
\text{148} & \quad + \quad \text{H}_2\text{C}=\text{C}<\text{CN} \\
\text{148} & \quad \xrightarrow{\text{hv}} \quad \text{151} \\
\text{150} & \quad + \quad \text{H}_2\text{C}=\text{C}<\text{CH}_3 \\
\text{148} & \quad \xrightarrow{\text{hv}} \quad \text{151} \\
\text{150} & \quad + \quad \text{H}_2\text{C}=\text{C}<\text{CN} \\
\end{align*}
\]
The photocycloaddition of thioparabanate (152) with various olefins (153) also generated the corresponding spirothietanes 154 (140).

\[ \text{152} \quad \text{153} \quad \text{154} \]

\[ R^1 = \begin{array}{c} \text{H} \\ \text{CH}_3 \end{array} \quad R^2 = \text{H}, \text{CH}_3 \quad R^3 = \text{COOCH}_3, \text{OC}_2\text{H}_5, \text{CH}_3 \quad R^4 = \text{H}, \text{CH}_3 \quad \text{or} \quad R^4R^5 = =\text{O}(\text{CH}_3)_2 \quad R^5 = \text{H} \]
SYNTHETIC APPROACH

The thietane derivatives investigated as potential analgesics were compounds 32-36. The synthesis of these compounds was approached through the corresponding

cyanothietanes 155-159 which were prepared according to the photochemical method described by Ohno and his coworkers (138). The general synthetic pathway established for

155 R=H
156 R=CH₃, cis
157 R=CH₃, trans

158 cis
159 trans
the synthesis of 32 is outlined in Scheme I:

Scheme I

Synthetic route to 2,2-diphenyl-3-dimethylaminomethylthietane 1,1-dioxide (32)

Replacing propenenitrile (144) with cis- and trans- 2-butenenitrile (162, 163) allowed the synthesis of
thietanes 156-159 which were the precursors of thietane 1,1-dioxides 33-36 respectively.

Generally, the synthesis of the desired products (32-36) was approached through 4 steps:

1. Preparation of the cyanothietanes by photocycloaddition of thiobenzophenone with appropriate olefinic nitrile
2. Preparation of cyanothietane 1,1-dioxides
3. Synthesis of aminomethylthietane 1,1-dioxides
4. Synthesis of N,N-dimethylaminomethylthietane 1,1-dioxides

During the course of synthesis of above thietane products, many related chemical reactions were performed in an attempt to solve the synthetic problems which were encountered, and to develop the present project. These will be described under the following additional titles:

5. Synthesis of 2,2-diphenyl-3-dimethylaminomethylthietane.
6. Attempted synthesis of thietane derivatives with the α-dimethylaminomethyl side chain
7. Chemical reactions of 2,4-diphenylthietane 1,1-dioxide and attempted synthesis of 2,4-diphenylthietan-3-one 1,1-dioxide
DISCUSSION

1. Synthesis of cyanothietanes by photocycloaddition of thiobenzophenone with olefinic nitriles

Thiobenzophenone (95) is a blue crystalline material which is very sensitive to atmospheric oxygen and easily undergoes polymerization at room temperature. It was prepared from benzophenone (164), in an amount as required, by a modification of the method of Grofton and Braude (141). Benzophenone (164) was treated with hydrogen sulfide in the presence of hydrogen chloride. The product was immediately purified by repeated recrystallization from n-pentane which was found to be a better solvent than the petroleum ether used by Grofton and Braude. With n-pentane, crystallization occurred in a shorter time and the purified thiobenzophenone was recovered in a better yield. Pure thiobenzophenone obtained after recrystallization for three or four times was stable in the freezer for a few months if the material was kept under nitrogen or carbon dioxide atmosphere. In most of the photocycloaddition reactions, freshly prepared thiobenzophenone was used. When
the stored thiobenzophenone was employed, it was further recrystallized three or four times.

The olefinic nitriles were commercially supplied. Propenenitrile (144) was obtained as a colorless liquid after fractionation through a Vigreaux column. Upon irradiation with unfiltered ultraviolet light generated from a medium pressure mercury arc, propenenitrile rapidly reacted with thiobenzophenone (95) to produce a white, unidentified polymer which was not soluble in common organic solvents. The 2-butenenitrile was obtained as a mixture of cis and trans isomers (162, 163) known commercially as crotononitrile. The analysis of this mixture by using gas liquid chromatography (glc) indicated that it contained 60-70% cis-2-butenenitrile (162) and 30-40% trans-2-butenenitrile (163) depending on the commercial sources. The boiling points (162: 108°, 163: 121°) of these two isomers were so close that they were not separated by fractionation through a 5 ft Vigreaux column. The systematically repeated fractionation (142) using a 2 ft column packed with glass helices also failed to separate the two isomers. The calculation based on the boiling point difference showed that a distillation column of at least 20 theoretical plates was required to achieve a 95% separation of two isomers (142). This meant that a column packed with 1/4 in x 1/4 in glass tubing and measuring at least 6 ft was needed for 95% separation. In order to obtain the separation of each isomer in a pure form, a column of higher efficiency was required.
A Spinning-Band-Column distillation apparatus, kindly made available by Mr. L. T. Muenster of the Chemistry department, The University of British Columbia, was selected for the separation of 162 and 163. The crotononitrile was repeatedly distilled until pure cis-2-butenenitrile and pure trans-2-butenenitrile were obtained. The purity of the separated isomers was confirmed by glc.

Irradiating a cyclohexane solution of thiobenzophenone (95) and propenenitrile (144) with ultraviolet light at the wavelength of 366 nm, generated a crude product which was purified by column chromatography to give pure 2,2-diphenyl-3-cyanothietane 155 as a white solid in

\[
\text{C}_7\text{H}_5\text{C} = \text{C} = \text{C} = \text{C} = \text{C} = \text{C} + \text{CH}_2 = \text{CHCN} \xrightarrow{366 \text{ nm}} \text{H} \text{C}_7\text{H}_5\text{C}_7\text{H}_5\text{C} = \text{C} = \text{C} = \text{C} = \text{C} = \text{C} \text{CN}
\]

95 144 155

a yield of 41%. The ir spectrum of 155 displays the absorption (2235 cm\(^{-1}\)) for the cyano group in addition to the signals for two phenyl substituents. The pmr spectrum of 155 is in agreement with the thietane structure. The two methylene protons (H\(_a\), H\(_b\)) are magnetically nonequivalent being displayed as two symmetrical, partly overlapping quartets centered at 3.32 and 3.47 ppm respectively. The methine proton (H\(_c\)) appears as a triplet at 4.99 ppm due
to two partly superimposing doublets. The geminal and the vicinal coupling constants \( J(H_a-H_b), J(H_a-H_c), J(H_b-H_c) \) are all equal to 9 Hz in comparison with the reported \( J(H_a-H_b) \) value of 10 Hz in compound 165 (139). The ten aromatic protons are displayed as a multiplet at 7.10-7.70 ppm. The conformation of 155 will be considered later.

The 41% yield of 155 was not the result of loss due to the purification process. Analysis by glc and thin layer chromatography methods indicated that crude product contained only 50% of 155 and at least four other components. Pure 155 was not soluble in n-pentane whereas about 40% of the crude mixture was soluble in this solvent. The n-pentane solution of the soluble components gradually became blue in colour suggesting the liberation of 95 from some unstable products. Evaporating this blue solution gave a greenish gummy substance with the characteristic odour of sulfide. Attempts were made to improve the yield of 155 by using acid-base washed 144, employing a new light filter, narrowing the band width of the isolated
light by using an additional light filter, shortening the irradiation time and using different proportions of 95 to 144. No significant improvement in the yield of 155 was observed. When the cyclohexane was replaced by anhydrous ether as solvent, the work-up was easier, due to the volatility of ether, and the crude reaction product obtained was a solid instead of a gummy substance, but the yield of 155 was comparable.

Ohno and his coworkers (138) in 1969 claimed that irradiating a mixture of 144 and 95 at 366 nm for four days resulted in a 93% yield of product. They did not specify whether this yield referred to the total crude product or the pure thietane 155. The photocycloaddition of 144 with 95 was re-examined by de Mayo and Shizuka (131) in 1973. Their data showed that the quantum yield in the formation of 155 was low and did not change with the irradiation time in the initial stage of reaction. The quantum yield for a substance under consideration is defined as the number of molecules that react or are formed in a photochemical process per number of photons absorbed in a unit of time. If every photon absorbed can initiate a molecule to undergo a certain chemical reaction, the quantum yield is unity. If other processes compete with the one under consideration, the quantum yield is much lower. The low quantum yield in the generation of thietane 155 implied that more than one single process occurred in the reaction of 95 with 144. In fact, it was discovered by de Mayo and
Schizuka (131) that thietane 155 was not the first-formed product but was derived from the thermal decomposition of an intermediate, 1,3-dithiane 166 which was isolated as a white solid in a 65% yield after irradiating a mixture of 95 and 144 at -78° (131). The dithiane 166 was relatively stable at low temperature. At 37° one mole of 166 liberated one mole of thietane 155 and one mole of 95 within a period of two days (131). Ohno and his coworkers (138) reported that the reaction of 95 and 144 did not occur at a longer wavelength (589 nm). On the contrary, de Mayo and Nicholson (130) isolated, in addition to thietane 155, 1,4-dithiane 167, benzothiane 168, and a disulfide derivative 169 after irradiating a mixture of 95 and 144 at wavelengths longer than 500 nm. Considering that so many photocycloaddition products were isolated and that the
yield of dithiane 166 in the reaction at 366 nm was only 65%, the reason of higher yield (93%) claimed by Ohno and his coworkers (138) for the photocycloaddition reaction of 95 with 144 is not clear. The 41% yield of 155 in our experiment supports the finding of de Mayo et al. that the thietane 155 was not the only product of the photochemical reaction. The other unidentified by-products were probably identical or similar to 167, 168 and 169. It was observed
that prolonged irradiation beyond the end point resulted in a poor yield of 155. This indicated that 155 was activated to undergo secondary photochemical reactions. Thus the 41% yield in the generation of 155 and the formation of other side-products after a long period of irradiation (about four days) is not surprising. Products such as 169 may be derived from the decomposition and further reaction of 155.

Irradiating a mixture of 95 and excess pure cis-2-butenenitrile (162) at 366 nm for 152 hours generated a mixture of cis-2,2-diphenyl-3-cyano-4-methylthietane (156) and cis-2,2-diphenyl-3-methyl-4-cyanothietane (158) in a ratio of 2.5:1, calculated on the basis of relative intensities of the two methyl signals in the pmr spectrum of

\[
\begin{align*}
\text{95} & \quad + \quad \text{162} \\
\text{366 nm} &
\end{align*}
\]
the reaction mixture. Analyzing the recovered excess butenenitrile by glc indicated that no isomerization of \textbf{162} to \textit{trans}-2-butenenitrile (163) occurred during 152 hours of irradiation. Only \textbf{162} was recovered from the photochemical reaction and no appreciable amount of \textit{trans}-isomer (163) was detected. The pmr spectrum of the reaction product showed two sets of signals that agreed with the data reported by Ohno et al. (138) for thietanes 156 and 158. The first set of signals was attributed to the thietane 156: The three methyl protons and H\textsubscript{a} were displayed as two doublets at 1.54 and 5.00 ppm respectively. The H\textsubscript{b} proton, coupling with its adjacent methyl protons and H\textsubscript{a}, was located as a multiplet centered at 3.80 ppm. From the signals of methyl protons and H\textsubscript{a} the coupling constants, $J(H_a-H_b)$ and $J(CH_3-H_b)$ were measured to be 8 and 7 Hz respectively in agreement with the corresponding coupling constants extracted from the H\textsubscript{b} multiplet. The 10 phenyl protons appeared as a multiplet at 7.10-7.75 ppm. The second set of signals agreed with the structure of 158. The doublets which were attributed to the methyl protons and the H\textsubscript{b} were located at 1.07 and 4.25 ppm respectively. The coupling constants, $J(H_a'-H_b')$ and $J(CH_3'-H_a')$, were also 8 and 7 Hz respectively. Similarly, H\textsubscript{a} coupling with the adjacent methyl protons and H\textsubscript{b}', appeared as a multiplet centered at 4.20 ppm.

When a mixture of \textit{trans}-2-butenenitrile (163)
and 95 was irradiated at 366 nm, a mixture of trans-2,2-diphenyl-3-cyano-4-methylthietane (157) and trans-2,2-diphenyl-3-methyl-4-cyanothietane (159) was obtained in a ratio of 2.8:1, calculated on the basis of the relative intensities of two methyl signals in the pmr spectrum. No isomerization of 163 to 162 during the reaction was observed. The pmr spectrum of the mixture showed two sets of signals that were compatible with the pmr data reported for 157 and 159 by Ohno and his coworkers (138). The first set of signals was attributed to the thietane 157: The three methyl protons and H_a were displayed as two doublets at 1.45 and 4.36 ppm respectively. The H_b proton, coupling with its adjacent methyl protons and H_a, was located as a
multiplet centered at 3.86 ppm. The 10 phenyl protons appeared as a multiplet at 6.8-7.8 ppm. The second set of signals agreed with the structure 159: The doublets which were attributed to the methyl protons and $H_b$ were located at 0.83 and 3.66 ppm respectively. The $H_a$ proton coupling with the adjacent methyl protons and $H_b$, appeared as a multiplet centered at 3.86 ppm and overlapping with the signals of $H_b$ in 157. The 10 aromatic protons were found in the region of 6.8-7.8 ppm. The coupling constants of corresponding protons in 157 were identical to those in 159, $J(CH_3-H)$ and $J(H-H)$ being 6 and 10 Hz respectively.

The photocycloaddition of 95 with olefins has been reported to be stereospecific (138). The configuration in the olefins was retained in the thietane products. Of the 2-butenenitriles (162, 163), the cis- and trans-isomers generated exclusively the cis- and trans- thietanes (156-159) respectively. The mechanism of the photocycloaddition reaction was proposed to involve the nucleophilic attack of the electron deficient olefins by the $\pi-\pi^*$ singlet species of 95. In the reaction of propenenitrile (144), the sulfur atom of 95 attacked the $\beta$-end of the double bond, resulting in formation of $\beta$-cyanothietane 155 while in the reactions of cis- and trans- 2-butenenitriles, the sulfur atom attacked both the $\alpha$- and $\beta$- carbons of the olefins (162, 163) to produce a mixture of $\alpha$-cyano- and $\beta$-cyano- thietanes (156-159). The latter reac-
tions were explained on the basis that electron deficiency at the \( \beta \)-carbons of 162 and 163 was somewhat weakened by the electron-releasing ability of the methyl group, and as a result, the orientation of photocycloaddition observed in the reaction with propenenitrile (144) no longer held in that with 2-butenenitriles (162, 163) (138).

de Mayo and Shizuka (131) showed that the formation of thietane 155 was derived from the thermal decomposition of the first-formed product 1,3-dithiane 166. The reaction between the \( \pi \rightarrow \pi^* \) singlet species of 95 and 144 was described to involve the generation of a zwitterion 170 which, upon formation, immediately associated with an additional molecule of 95 resulting in the formation of
1,3-dithiane which liberates one molecule of each of thietane and thiobenzophenone at room temperature. It is not known whether the formation of thietanes from 162 and 163 also involved the thermal decomposition of similar intermediates (171, 172).

Attempts to separate the α-cyanothietanes (158, 159) and the β-cyanothietanes (156, 157) from their isomeric mixtures were carried out by crystallization and chromatography methods but without success. The isomeric mixtures of α- and β-cyanothietanes were then oxidized with the hope that separation of the α- and the β-cyano isomers could be achieved at their sulfone stage. Thietane 1-oxides and thietane 1,1-dioxides are usually more stable
and of higher melting point than the parent compounds.

2. **Synthesis of cyanothietane 1,1-dioxides**

When thietane 155 was treated with m-chloroperoxybenzoic acid (173), the expected product, 2,2-diphenyl-3-cyanothietane 1,1-dioxide (160), was obtained. The ir spectrum of 160 showed the absorptions of sulfone (1143 and 1325 cm\(^{-1}\)) and nitrile (2265 cm\(^{-1}\)). In the pmr spectrum of 160, the two methylene protons and the methine proton appeared as a multiplet centered at 4.63 ppm, and the ten phenyl protons appeared as a multiplet at 7.43 ppm. The coupling constants could not be measured because of the complexity of the spectrum.

Similar treatment of a 2.5:1 mixture of 156 and 158 with 173 gave a 68.4% yield of cis-2,2-diphenyl-3-cyan-4-methylthietane 1,1-dioxide (174). The \(\alpha\)-cyano isomer, 175, was not detected in the reaction mixture, indicating that thietane 158 or sulfone 175 did not survive the oxidation reaction. The structure of 174 was assigned according to the spectroscopic data and elemental analysis, and
was supported by the yield of 174 in the oxidation reaction. The ir spectrum of 174 showed stretchings of sulfone (1155 and 1330 cm\(^{-1}\)) and nitrile (2260 cm\(^{-1}\)) in addition to the phenyl and carbon-hydrogen vibrational absorptions. The 60 mHz pmr spectrum of 174 displayed signals for three methyl protons (1.63 ppm), a multiplet for the ring methine protons \(H_a\) and \(H_b\) (4.40-4.80 ppm) as well as absorptions for 10 phenyl protons (7.20-7.60 ppm). High-order splitting was observed in the multiplet of \(H_a\) and \(H_b\) due to small difference in the chemical shifts of these two protons and their coupling with the methyl protons. The high-order coupling effect was also observed in the methyl absorptions which appeared as an abnormal triplet with the middle peak
shorter than the outer peaks by a half of their intensities (Figure II). In the 100 mHz pmr spectrum, this abnormal triplet tended to become a doublet and the multiplet of H\textsubscript{a} and H\textsubscript{b} was composed of more peaks than in the 60 mHz spectrum. In order to measure the vicinal coupling constant, J(H\textsubscript{a}-H\textsubscript{b}), spin-decoupling was employed. When the methyl signal at 1.63 ppm was irradiated, the multiplet at 4.40-4.80 ppm collapsed to form an AB quartet centered at 4.57 ppm. The vicinal coupling constant, J(H\textsubscript{a}-H\textsubscript{b}), and the chemical shift difference, \Delta\nu(H\textsubscript{a}-H\textsubscript{b}) were found to be 9 Hz and 4.6 Hz respectively. The small \Delta\nu/J ratio thus was the cause of the complexity of the methyl signal and the multiplet of two ring methine protons. Virtual coupling between the methyl protons and H\textsubscript{a} occurred (143).

The yield of sulfone in the oxidation of the isomeric mixture of thietanes \textsubscript{156} and \textsubscript{158} excluded the possibility that the product formed was sulfone \textsubscript{175}. If the oxidation product isolated had been the sulfone \textsubscript{175}, the yield of product would have been only 59% of the quantity of the pure sulfone \textsubscript{174} actually isolated, according to the calculation of a 100% yield of sulfone \textsubscript{175} on the basis of a 2.5:1 mixture of thietanes \textsubscript{156} and \textsubscript{158} used in the oxidation reaction. The yield of the isolated sulfone exceeded the possible maximum yield of sulfone \textsubscript{175} in a quantity of 41%.

When a 2.8:1 mixture of trans isomeric thietanes
Figure II

Pmr spectrum of cis-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide (174) dissolved in CDCl₃
157 and 159 was oxidized by peracid 173, trans-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide (176) was isolated in 58.7% yield. The \( \alpha \)-cyano isomer, trans-2,2-diphenyl-3-methyl-4-cyanothietane 1,1-dioxide (177), unfortunately was not detected in the reaction mixture, indicating that thietane 159 or sulfone 177 did not survive the oxidation reaction. The structure of sulfone 176 was assigned according to the spectroscopic data and the elemental analysis, and was supported by the yield of 176 isolated from the oxidation reaction. The ir spectrum of sulfone 176 showed absorptions of sulfone (1148 and 1318 cm\(^{-1}\)) and nitrile (2260 cm\(^{-1}\)). The pmr spectrum of sulfone 176, un-
like that of sulfone 174, showed a first-order spectrum for the methyl and the ring methine protons. The 10 phenyl protons were displayed as a multiplet at 7.42 ppm. The proton H_b, coupling with the methyl protons and H_a, appeared as two partly overlapping quartets centered at 4.83 and 5.01 ppm respectively. The proton H_a and the methyl protons were displayed as two doublets at 3.78 and 1.63 ppm respectively. The vicinal coupling constants, J(CH_3-H_b) and J(H_a-H_b), were equal to 7 Hz and 10 Hz respectively.

The yield of sulfone in the oxidation of the isomeric mixture of thietanes 157 and 159 excluded the possibility that the product formed was sulfone 177. If the oxidation product isolated had been the sulfone 177, the yield of product would have been 50% of the quantity of the pure sulfone 176 actually obtained according to the calculation of a 100% yield of sulfone 177, on the basis of a 2.8:1 mixture of thietanes 157 and 159 used in the oxidation reaction. The yield of the isolated sulfone exceeded the possible maximum yield of 177 in a quantity of 50%.

The oxidation of cis-\(\alpha\)-cyanothietane 158 and trans-\(\alpha\)-cyanothietane 159 did not produce the expected sulfones. As previously mentioned in the Thietane Chemistry section, the electronic nature and the bulkiness of substituents on the thietane ring determine whether the \(\alpha\)-
cyanothietane 1,1-dioxide can be formed. The presence of two bulky phenyl groups and the lack of a 4-methyl substituent that can compensate for the electron-withdrawing effect of the sulfone function may lead to breakdown of sulfone 175 if it was formed. One of the possible paths of degradation is the reversed process of cyclization of sulfene and olefin.

\[
\begin{align*}
\text{CH}_3 & \quad \text{H} \\
\text{NC} & \quad \text{SO}_2 \\
\text{H} & \\
\end{align*}
\rightarrow
\begin{align*}
\text{NC} & \quad \text{C}=\text{SO}_2 \\
\text{H} & \\
\text{CH}_3 & \quad \text{C}=\text{C} \\
\end{align*}
\]

In the oxidation of thietanes 155-157 to sulfones 160, 174 and 176, chloroform or methylene chloride was used as solvent. When anhydrous ether was used as solvent in the oxidation of a mixture of cis thietanes 156 and 158, precipitation of a white solid soon occurred after the addition of peracid 173. The white solid was
identified as cis-2,2-diphenyl-3-cyano-4-methylthietane 1-oxide (178) according to its spectroscopic data and subsequent oxidation to 174. Obviously, the formation of sulfoxide 178 was due to its low solubility in ether. Therefore further oxidation to sulfone 174 was prevented by immediate precipitation of the sulfoxide upon its formation.

When a mixture of trans thietanes 157 and 159 was oxidized in an identical condition, the precipitation of the expected trans thietane 1-oxide did not occur. The solubility of trans-2,2-diphenyl-3-cyano-4-methylthietane 1-oxide might be higher in ether so that the oxidation carried on until the sulfone stage was reached. It was also possible that the rate of reaction in oxidation of cis sulfoxide to cis sulfone was slower than that of the trans isomer, probably because of the steric effect of the ring substituents. The oxidation of thietanes to thietane 1,1-dioxides in fact proceeded very fast in chloroform. Stirring a chloroform solution of peracid 173 and a thietane mixture of 156 and 158 or of 157 and 159 generated 174 or 176 in the expected good yield within one or two hours.

In the ir spectrum of 178, the characteristic sulfoxide and nitrile absorptions appeared at 1080 and 2260 cm$^{-1}$ respectively, and no sulfone band was observed. The pmr spectrum of 178 showed a multiplet for 10 phenyl protons (7.40 ppm), a doublet for proton $H_a$ (4.71 ppm),
two overlapping quartets of a doublet for proton $H_b$ (3.41 ppm), and a doublet for three methyl protons (1.67 ppm). The vicinal coupling constants, $J(H_a-H_b)$ and $J(CH_3-H_b)$ were 10 and 7 Hz respectively.

3. Synthesis of 3-aminomethylthietane 1,1-dioxides

In consideration of the inherent nature of thietane derivatives to undergo ring opening reactions, only limited methods were considered suitable to convert the cyano-thietane 1,1-dioxides 160, 174 and 176 to the corresponding aminomethyl derivatives (161, 179, 180). It had been reported from our laboratory (84) that sponge nickel catalyst under mild conditions (room temperature, 50 psi $H_2$) catalyzed the conversion of 2,4-diphenyl-3-cyanothietane 1,1-dioxide (181) to the corresponding 2,4-diphenyl-3-aminomethylthietane 1,1-dioxide. Attempts to hydrogenate 160 by this method, however, resulted in recovery of unreacted starting material. When the hydrogenation was per-
formed under relatively vigorous conditions by using Raney nickel, co-catalysts (sodium acetate and acetic anhydride), higher temperature (90°), and 50 psi H₂, desulfonation of the sulfone 160 occurred.

The reduction of nitriles 160, 174 and 176 was achieved by using diborane. Conversion of 3-cyanothietane 1,1-dioxides (183) to the corresponding 3-aminomethylthietane 1,1-dioxides (184) by using this mild, acidic, reducing agent had been reported from our laboratory (84, 85). The method involved the hydroboration, for one day, by using excess diborane (144), and the subsequent hydrolysis of the intermediate formed. The latter step was accom-
plished by treating the reaction mixture with ethanol followed by refluxing the resulting solution for one hour. It had been reported that diborane reduced a variety of functional groups but did not react with sulfide or sulfone (144). The mechanism of diborane reduction of nitrile involves the formation of a borane-nitrogen bond and the transfer of hydride ion (145). The preliminary reaction product is therefore a borane adduct such as \( N,N,N \)-tri-alkylborazine (185) (144). The isolation of primary amine consequently requires hydrolysis of the borane interme-
diolate. Some of the borane-nitrogen complexes are quite stable and must be subjected to strong acidic hydrolysis.

\[
\text{RCN} + 3\text{BH}_3 \rightarrow \text{RCH}_2\text{N\textsuperscript{2+}}\text{BH}^+ \text{BH} \quad \text{185}
\]

For instance, borane-trimethylamine complex in water-glycol solution containing 1M HCl required a period of six hours for complete hydrolysis (146).

In an attempt to reduce nitrile 160 by using the above described diborane method, 160 was treated with diborane, the excess hydride was destroyed by adding ethanol, and the resulting ethanolic solution was hydrolyzed by refluxing on a steam bath for one hour. Work-up of the reaction mixture afforded a gummy substance of which the ir spectrum showed the loss of characteristic absorptions of nitrile and sulfone groups, indicating that the CN group was successfully reduced, but with apparent sacrifice of the thietane ring. When the diborane reduction was similarly repeated but the refluxing step omitted to prevent thermal desulfonation of the expected product, the ir spectrum of the crude reduction product confirmed the absence of the CN group, and displayed strong absorptions for SO\textsubscript{2}
and BH groups. These results indicated that the borane adduct was formed in the reaction, and that hydrolysis was necessary to generate the amine under conditions which would not destroy product.

The liberation of primary amine from the borane adduct without destruction of thietane ring was found to be successful by hydrolyzing the borane adduct in aqueous hydrochloric acid at room temperature for two days. The hydroboration with freshly generated diborane generally gave a good yield of the expected primary amine after the acid-catalysed hydrolysis process. The use of stored solutions of diborane in tetrahydrofuran, however, resulted in high yields of borane adduct but low yields of primary amine, probably due to the formation of more stable borane complexes which were more resistant to the mild hydrolysis process used.

Schematically, the conversion of nitrile 160, 174 and 176 is shown as follows:

160 $R=H$
174 $R=\text{CH}_3$, cis
176 $R=\text{CH}_3$, trans
The diborane reduction of 160 gave the expected primary amine 161. The ir spectrum of 161 showed absorptions for NH$_2$ (3300 and 3360 cm$^{-1}$) and SO$_2$ (1135 and 1310 cm$^{-1}$). Treating 161 with acetic anhydride gave the corresponding amide, 2,2-diphenyl-3-(acetamidomethyl)thietane 1,1-dioxide (186), as needle-like crystals. The ir and pmr spectra agreed with the structure 186. The mono-substituted amide absorption appeared at 3425 (N-H) and 1675 (C=O) cm$^{-1}$ whereas strong sulfone bands occurred at 1145 and 1300 cm$^{-1}$. The pmr spectrum of 186 displayed a singlet for
three methyl protons, a multiplet (2.72-4.28 ppm) for 3 ring protons (Hₐ, Hₐ) together with two methylene protons adjacent to the amide function, a broad triplet (5.70-6.10 ppm) for the NH proton and a multiplet (7.10-7.65 ppm) for the ten phenyl protons. The complexity of the spectrum precluded the measurement of the coupling constants. Treating 161 with picric acid gave a picrate salt of 161. The ir and pmr spectra agreed with the structure.

The diborane reduction of nitrile 174 gave the expected primary amine 179 as needle-like crystals. The ir spectrum of 179 showed the absorption for NH₂ (3325 and 3385 cm⁻¹) and SO₂ (1140, 1155 and 1300 cm⁻¹) groups. The pmr spectrum of 179 displayed a broad, D₂O-exchangeable singlet for the amino protons (0.98 ppm), a doublet for three methyl protons (1.53 ppm) and a broad distorted doublet for two N-methylene protons (2.89 ppm). Protons Hₐ (3.50 ppm), Hₐ (4.53 ppm) and 10 phenyl protons (7.42 ppm) were displayed as 3 sets of multiplets. The coupling constants were: J(Hₐ-Hₐ)=9 Hz; J(CH₃-Hₐ)=7 Hz and J(CH₂-
Treating the primary amine 179 with picric acid generated a yellow picrate salt. The ir and pmr spectra were in accord with the structure expected.

The diborane reduction of nitrile 176 generated the expected primary amine 180. The ir spectrum of 180 showed the absorptions for NH$_2$ (3320 and 3380 cm$^{-1}$) and SO$_2$ (1145 and 1303 cm$^{-1}$) groups. Treating 180 with acetic anhydride gave the corresponding N-acetyl derivative 187. The ir spectrum of 187 showed the mono-substituted amide absorptions (1650 and 3330 cm$^{-1}$) in addition to the strong sulfone bands (1145 and 1300 cm$^{-1}$). The pmr spectrum of 187 displayed a doublet for three ring methyl protons (1.52 ppm), a singlet for three methyl protons adjacent to the carbonyl group (1.83 ppm), a multiplet for two N-methylene protons together with proton H$_a$ (2.93-3.37 ppm), a multiplet for proton H$_b$ (4.40 ppm), a broad triplet for NH proton (5.40 ppm) and a strong signal for 10 phenyl protons (7.38 ppm). The coupling constants were: $J$(CH$_3$-H$_b$)=7 Hz; $J$(H$_a$-H$_b$)=9 Hz. Treating the primary amine 187 with picric
acid generated the corresponding picrate salt with pmr data in agreement with the expected structure.

4. Synthesis of 3-dimethylaminomethylthietane 1,1-dioxides

It has been reported that 3-aminomethylthietane 1,1-dioxides (184) could be dimethylated using the Eschweiler-Clark procedure which involved heating the amines in a mixture of formaldehyde and formic acid (84, 85). The reaction probably proceeds through the formation of an amine alcohol or an imine which is subsequently reduced by formic acid. The first step can be affected by such cata-

\[
\begin{align*}
\text{RNH}_2 + \overset{\text{C}=0}{\overset{\Delta}{\longrightarrow}} & \text{RNH} \overset{\text{C}=\text{OH}}{\overset{-\text{H}_2\text{O}}{\longrightarrow}} \text{RN} \overset{\text{C}=\text{H}}{\overset{\text{HCOOH}}{\longrightarrow}} \\
\text{RNHCH} & \\
\overset{\text{R}^1, \text{NH}}{\overset{\text{R}^2, \text{N}}{\overset{\text{R}^2}{\longrightarrow}}} \overset{\text{R}^1, \text{C}=\text{O}}{\overset{\text{R}^2, \text{N}=\text{OH}}{\longrightarrow}} & \overset{\text{R}^1, \text{N}=\text{C}=\text{H}}{\overset{\text{HCOOH}}{\longrightarrow}} \\
\end{align*}
\]

184  R=H; benzene; benzene-Cl; benzene-NO₂
lysts as pyridine, ammonia, and urea, whereas the second step, the reduction of amine alcohol or Schiff's base, has been found, in some reactions, to be affected more by heat than by other means. Methylation of ammonia to trimethylamine, for example, proceeded in a good yield by heating the formaldehyde and ammonia without addition of formic acid (147).

When 2,2-diphenyl-3-aminomethylthietane 1,1-dioxide (161) was heated in a mixture of formic acid and formaldehyde (30%) at 90°, desulfonation occurred as indicated by the lack of sulfone absorptions in the ir spectrum of the reaction product. The heating was believed to be the cause of desulfonation during the dimethylation process.

Among other mild methods of N-dialkylation, catalytically reductive alkylation was found to be the most suitable method to synthesize the expected dimethylamines 32–34 from their corresponding primary amines 161, 179 and 180. The method involves the catalytic hydrogenation of a
mixture of amine and carbonyl compound and has been well documented for preparing secondary or tertiary amines (147). The reaction intermediate is also believed to be the amine alcohol or the imine which is catalytically hydrogenated, resulting in the formation of the secondary or tertiary amine. By using formaldehyde, for example, the alkylation of a primary amine may lead to N-methylation or N,N-dimethylation, depending on the quantity of formaldehyde used. The efficiency of the alkylation depends on the
ease with which aldehyde or ketone reacts with amine to form a reducible intermediate. The basicity of the amine group is thus a factor. When two amino groups are present in the same molecule, the more basic one is expected to undergo preferential alkylation.

Various different kinds of catalyst have been used for the reduction. Raney nickel and palladium are two of the most common catalysts used. In consideration of the ability of the Raney nickel to cause desulfonation of sulfones and the capacity of palladium to catalyze low-pressure hydrogenation at room temperature, palladium on charcoal was considered to be the best choice for the dimethylation of 3-aminomethylthietanes 161, 179 and 180. It is known that the amine itself may have a poisonous effect on the catalyst. Addition of an equivalent amount of weak acid such as acetic to the hydrogenation mixture has been suggested to neutralize the effect of base and thus facilitate the low pressure reductive alkylation (147).

The reductive dimethylation of primary amines 161, 179 and 180 gave the desired products 32-34. The ir spectra showed typical absorptions for the sulfone group in the range of 1135-1300 cm⁻¹ and the lack of N-H stretching, confirming the presence of tertiary amino structure. The
pmr data were in accord with the structures of 32-34, N-dimethylamino group absorption appearing in the range of 2.1-2.2 ppm. The products were further characterized as picrate salts.

The hydrochloride salt of 33 was not stable in chloroform solution. When a sample of 33 was dissolved in chloroform, an insoluble material rapidly crystallized out from the solution in one or two minutes. This unidentified crystalline substance, different from the original material, was insoluble in common laboratory solvents. Ir spectrum showed the absorptions for sulfone and ammonium groups.

The configurations of 33 and 34 were assigned in terms of those of their nitrile precursors since neither diborane reduction nor reductive alkylation would be expected to produce any isomerization of the ring substituents. It is not possible to apply Karplus correlation (148, 149) to assign conformations for 33 and 34 since both cis and trans vicinal coupling of ring protons of these compounds and their precursors are not discriminatory in magnitude (Table II). This result was not unexpected considering the reported values for cis and trans coupling in thietane derivatives (138, 150). Inspection of the vicinal coupling constants listed in Table III reveals that $J(2\alpha x-3eq)$ and $J(2eq-3\alpha x)$ in the cis and $J(2\alpha x-3\alpha x)$ in the trans coupling have similar and larger values whereas $J(2eq-3eq)$ in the trans coupling is discernibly smaller.
Table II

Vicinal coupling constants, $J(H_a-H_b)$, of 2,2-diphenylthietane derivatives

\[
\begin{align*}
\text{Compound} & \quad R_1 & \quad R_2 & \quad J(H_a-H_b), \text{ Hz} \\
156 & {} & \text{cis CN} & 8 \\
157 & {} & \text{trans CN} & 10 \\
178 & 0 & \text{cis CN} & 10 \\
174 & 0_2 & \text{cis CN} & 9 \\
176 & 0_2 & \text{trans CN} & 10 \\
179 & 0_2 & \text{cis CH}_2\text{NH}_2 & 9 \\
188 & 0_2 & \text{cis CH}_2\text{NH}_2 \text{ picrate} & 9 \\
189 & 0_2 & \text{trans CH}_2\text{NH}_2 \text{ picrate} & 9 \\
187 & 0_2 & \text{trans CH}_2\text{NHCCH}_3 & 9 \\
177 & 0_2 & \text{cis CH}_2\text{N(CH}_3)_2 & 9 \\
190 & 0_2 & \text{cis CH}_2\text{N(CH}_3)_2 \text{ picrate} & 9 \\
34 & 0_2 & \text{trans CH}_2\text{N(CH}_3)_2 & 10
\end{align*}
\]
Table III

Vicinal coupling constants (Hz) of thietane derivatives (150)

<table>
<thead>
<tr>
<th></th>
<th>J(cis)</th>
<th>J(trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>J(2ax-3eq)</td>
<td>J(2eq-3ax)</td>
</tr>
<tr>
<td>Thietane 1,1-dioxide</td>
<td>10.34</td>
<td>6.33</td>
</tr>
<tr>
<td>Thietane 1-oxide</td>
<td>10.63</td>
<td>7.49</td>
</tr>
<tr>
<td><strong>Trans</strong>-2,4-diphenylthietane 1-oxide</td>
<td>10.24</td>
<td>8.79</td>
</tr>
<tr>
<td><strong>Cis</strong>-2,4-diphenylthietane 1-oxide</td>
<td>9.53</td>
<td>-</td>
</tr>
<tr>
<td><strong>Trans</strong>-2,4-diphenylthietane 1,1-dioxide</td>
<td>9.17</td>
<td>-</td>
</tr>
<tr>
<td>3-Substituted thietane 1,1-dioxides</td>
<td>7.5-8.3</td>
<td>-</td>
</tr>
<tr>
<td>Thietane 3-carboxylic acid 1-oxide</td>
<td>10.84</td>
<td>-</td>
</tr>
<tr>
<td>Thietane 3-carboxylic acid</td>
<td>-</td>
<td>8.04</td>
</tr>
<tr>
<td>3-chlorothietane</td>
<td>-</td>
<td>7.67</td>
</tr>
</tbody>
</table>
The large $J(H_a-H_b)$ values of 9-10 Hz (Table II) in trans-2,2-diphenyl-4-methylthietane derivatives 34, 157, 176, 187 and 189 thus suggested that both the 3-substituent and the 4-methyl group possessed an equatorial orientation so that a trans 2,3-diaxial coupling occurred. For 2,2-diphenyl-3-cyanothietane (155), the value of 9 Hz found for

![Chemical structure](image)

both cis and trans vicinal coupling suggested, on the same basis, an equatorial orientation of the 3-cyano group. The other possible conformation having an axial cyano group
orientation, can be expected to result in a large $J(2\text{ax}-3\text{eq})$ but a small $J(2\text{eq}-3\text{eq})$ value. In the $\text{cis}-2,2\text{-diphenyl-4-methylthietane derivatives (33, 156, 174, 178, 179, 188 and 190),}$ the magnitude of $J(H_a-H_b)$ values could not be related to their stereochemistry since both $J(2\text{ax}-3\text{eq})$ and $J(2\text{eq}-3\text{ax})$ can be expected to have similar values (Table III). It is, nevertheless, reasonable to consider that both 32 and 33 possess equatorial orientation of the amino substituent since non-bonding interactions are expected to be less in such a conformation.

![Chemical structures](image)

5. **Synthesis of 2,2-diphenyl-3-dimethylaminomethylthietane (191)**

Since the synthetic route to 2,2-diphenyl-3-dimethylaminomethylthietane 1,1-dioxides (32-34) from their 3-cyano precursors (155-157) had been established, it was considered that preparation of 2,2-diphenyl-3-dimethylaminomethylthietane (191) from their 3-cyanothietane derivative (155) by employing the same method might be of in-
terest in consideration that the sulfone group in the compounds 32-34 might cause steric hindrance to their binding to the analgesic receptor. Although the sulfone analogue of methadone (23) was found (16) to be as active as methadone (14), the sulfone group in the semi-rigid thietane derivatives 32-34 was not expected to have the same flexibility as that in 23. The restricted sulfone group thus might affect the binding of compounds 32-34 to the receptor and consequently result in the loss of analgesic activity. The removal of two oxygen atoms from the sulfinyl sulfur may result in compounds with significant change in lipophilicity. Whether this change will affect the analgesic activity of the new compounds is also an interesting problem.

When 3-cyanothietane derivatives 155 was reduced with borane dimethyl sulfide complex, the primary amines 193 was generated. Catalytic reductive dimethylation of 193
using formaldehyde did not afford the expected dimethylamine 191.

An alternate route to 191 was carried out by using repeated formylation and reduction (151). The method involved the preparation of a formamide, which was subsequently reduced by using lithium aluminum hydride. When primary amine 155 was formylated with formic-acetic anhydride, a formamide (195) was obtained as evidenced by the characteristic absorptions of C=O (1675 cm⁻¹) and N-H (3300 cm⁻¹) in the IR spectrum of the product. Treating this formamide (195) with lithium aluminum hydride at 0° yielded a secondary amine (196) for which the IR spectrum confirmed the reduction of the carbonyl group and showed an absorption for N-H stretching (3310 cm⁻¹). When similar formylation and reduction procedures were performed on 196, the dimethylated product 191 was generated. Treating the ter-
Tertiary amine 191 with HCl gave a crude hydrochloride salt (197) of 191, which displayed characteristic ammonium absorptions in its ir spectrum. The pmr spectrum of 197 showed a singlet for six N-methyl protons (2.73 ppm), a multiplet (2.35-3.40 ppm) for two N-methylene protons and two ring α-methylene protons, a multiplet (4.10 ppm) for one methine proton and a singlet for ten phenyl protons (7.33 ppm). The ammonium proton was displayed as a D₂O exchangeable broad singlet at 5.88 ppm.

It had been reported that olefins which were substituted by electron releasing groups (e.g. 136, 202, 204), on irradiation with either 366 nm or 589 nm light, reacted with thiobenzophenone (95) to form either dithiane (e.g.
or thietane derivatives (e.g. 203, 205) depending on the steric factor (138). An attempt to generate 191 using

\[
\text{CH}_2=\text{CH}-\text{OC}_2\text{H}_5 + 95 \xrightarrow{\text{hv}}_366 \text{ or } 589 \text{ nm} \rightarrow \text{C}_6\text{H}_5\text{O} \]

136

\[
\text{CH} = \text{CH}-\text{CH}_3 + 95 \xrightarrow{\text{hv}}_366 \text{ nm} \rightarrow \text{H} \]

202

\[
\text{CH}_3 \xrightarrow{\Delta} \text{H}_2\text{CO}, \text{HCOOH} \rightarrow \text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{NH}_2 \rightarrow \text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{N}<\text{CH}_3 \]

199

200

this simple procedure by irradiating a mixture of N,N-di­methyldiallylamine (200) and thiobenzophenone (95) was without success.
6. Attempted synthesis of thietane derivatives with α-dimethylaminomethyl side chain

As mentioned previously, methadone existed in a preferred conformation in which a close approach of the tertiary amine group to the oxygenated function was observed. In two studies (84, 85) of thietane derivatives as potent analgesics, it was suggested that an α-dimethylaminomethyl side chain might be required for the analgesic activity. A close approximation between amino group and sulfone function might be achieved (84, 85) in compounds 35, 36, and 206-208. The precise location of the amino group and
the orientation of the unbonded electron pair of nitrogen in narcotic analgesics have been reported to be important to their analgesic activity. Compounds 207, 36 and 206-208 thus might be valuable in the study of structure-activity relationships with comparisons in particular to the thietane derivatives having a β-amino side chain (32-34 etc.).

Haya (85) had attempted the synthesis of 206 by reacting sulfonyl chloride 79 with enamine 209 but isolated an acyclic sulfone instead of the desired cyclic product 210.
Since attempts to prepare cis- and trans-2,2-diphenyl-3-methyl-4-dimethylaminomethylthietane 1,1-dioxide (35, 36) were frustrated by difficulties encountered in the synthesis of the precursors, 175 and 177, the synthesis of compounds 207 and 208 was considered and approached according to the following scheme:

\[
\begin{align*}
\text{HOCH}_2\text{CH}_2\text{SH} & \xrightarrow{\text{Cl}_2, \text{H}_2\text{O}} \text{ClCH}_2\text{CH}_2\text{SO}_2\text{Cl} \\
\text{(Et)}_3\text{N} & \xrightarrow{\text{C}_6\text{H}_5-\text{CH}=\text{CHN(CH}_3)_2} \\
\end{align*}
\]

\begin{align*}
211 & \quad 212 & \quad 213 \\
\end{align*}

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} & \quad \text{CH}_2\text{Cl} & \quad \text{SO}_2 \\
\quad & \quad & \quad & \quad \\
\end{align*}
\]

\begin{align*}
\text{CH}_3 & \quad \text{N} & \quad \text{CH}_2\text{Cl} & \quad \text{SO}_2 \\
\quad & \quad & \quad & \quad \\
\end{align*}

\begin{align*}
\text{CH}_3 & \quad \text{N} & \quad \text{CH}_2\text{Cl} & \quad \text{SO}_2 \\
\quad & \quad & \quad & \quad \\
\end{align*}

\begin{align*}
\text{CH}≡\text{CCH}_2\text{OH} & \xrightarrow{(\text{CH}_3)_2\text{SO}_4} \text{CH}≡\text{CCH}_2\text{OCH}_3 & \xrightarrow{\text{NaOBU}} \\
\end{align*}

\begin{align*}
217 \\
\end{align*}
The cycloaddition of electron rich olefins with sulfenes generated from sulfonyl chlorides has been described in the introduction section. It was expected that the reaction between the α-chloroethanesulfonyl chloride (212) and α-dimethylaminostyrene (213) in the presence of triethylamine would generate the cycloadduct 214 which could then be converted to the final product 207.

The sulfonyl chloride 212 was prepared, according to a method taken from a patent (152), by reacting α-mercaptoethanol (211) with chlorine and water. The α-dimethylaminostyrene (213) was prepared according to the procedure described by Coates (84a) from phenylacetaldehyde and dimethylamine.
When a mixture of 213 and triethylamine in an equimolar amount was treated with 212, the product isolated was not the expected cyclic adduct 214 but a mixture of an acyclic compound, α-(vinylsulfonyl)-β-dimethylaminostyrene (218), and triethylamine hydrochloride. The triethylamine hydrochloride formed was quantitative (0.03 mole) when the amount of sulfonyl chloride (212), enamine (213) and triethylamine used were 0.015, 0.015 and 0.03 moles respectively, indicating that the two chlorine atoms in 212 were removed by two molecules of triethylamine and that generation of compound 214 containing a chloromethyl group α to the sulfonyl function was not possible in this reaction. The ir spectrum of 218 showed strong absorptions of enamine (1620 cm\(^{-1}\)), sulfone (1120, 1135 and 1300 cm\(^{-1}\))
and vinylic C-N (1185 and 1258 cm$^{-1}$) functional groups. The pmr spectrum of 218 displayed a sharp singlet for six dimethylamino protons (group a, 2.68 ppm), an ABX multiplet for three vinylic protons (group b, 5.50-6.80 ppm) and two singlets for five phenyl protons (7.33 ppm) and one enamine proton Hc (7.37 ppm). These data are compared well with those reported for the analogous compounds 222, 223 (153) and 221 (84). The same vinyl enamino sulfone 218 was also isolated by Paquette and Rosen in a yield of only 6% upon treating thietane 219 with methanesulfonyl chloride and triethylamine (153). The pmr signals

![Chemical structure](image)

of 218, however, were not correctly assigned. A value of 5.94 ppm was reported by these workers for the chemical shift of the =CHN proton and was not consistent with those $\delta$-values reported for compounds 221-223 (Table IV). A singlet at 6.00 ppm was indeed present in the pmr spectrum of 218 but was part of the ABX multiplet of the three CH$_2$=CHS protons.

It has been known that reactions of sulfenes and
Table IV

Chemical shifts (ppm) of sulfonyl enamines (84, 153)

<table>
<thead>
<tr>
<th></th>
<th>C$_6$H$_5$=</th>
<th>NCH=</th>
<th>N(CH$_3$)$_2$</th>
<th>CH$_2$=CHS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_6$H$_5$-CH$_2$-SO$_2$=C=CHN(CH$_3$)$_2$ (221)</td>
<td>7.41</td>
<td>7.22</td>
<td>2.60</td>
<td>-</td>
</tr>
<tr>
<td>CH$_2$=CH-SO$_2$=CH=CHN(CH$_3$)$_2$ (222)</td>
<td>-</td>
<td>7.18</td>
<td>2.92</td>
<td>5.73(d)</td>
</tr>
<tr>
<td>CH$_3$-CH$_2$-SO$_2$-C=CHN(CH$_3$)$_2$ (223)</td>
<td>7.22</td>
<td>7.14</td>
<td>2.59</td>
<td>6.10(d)</td>
</tr>
<tr>
<td>CH$_2$=CH-SO$_2$=C=CHN(CH$_3$)$_2$ (218)</td>
<td>7.33</td>
<td>7.37</td>
<td>2.68</td>
<td>6.68(q)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.5-6.8(m)</td>
</tr>
</tbody>
</table>

* d: doublet, q: quartet, m: multiplet
enamines can give either thietanes or acyclic substitution products depending on the nature of reactants. A two-step mechanism (Page 36) is generally favored (112-117) on the basis of Woodward-Hoffman selection rules (154), the stereoselectivity in the formation of products and the nucleophilic nature of olefins used (106). It appears that the nature of the product was governed by electronic and steric factors that influence the Zwitterion \( Z \). Any electronic effect which stabilizes \( Z \) or any steric hindrance which obstructs the intramolecular cyclization of \( Z \) will facilitate the formation of acyclic product. The isolation of acyclic product 218 in the attempted cycloaddition reaction was probably due to the intramolecular dehalogenation of the Zwitterion 224. The absence of cyclic product in this case attests to the facile nature of the dehalogenation.

\[
\begin{align*}
\text{ClCH}_2\text{C(SO}_2\text{)}\text{H} + \text{CH}_3\text{N}=\text{C(=O)}\text{H} & \rightarrow \text{CH}_3\text{N}=\text{C(=O)}\text{H} \rightarrow \text{CH}_2=\text{CH-SO}_2 \\
\text{CH}_3\text{N}=\text{C(=O)}\text{H} & \rightarrow \text{CH}_3\text{N}=\text{C(=O)}\text{H} \rightarrow \text{CH}_2\text{C(SO}_2\text{)}\text{ClCH}_2
\end{align*}
\]
As the desired product, 214, could not be prepared by this route, synthesis of 207 was abandoned, and the attempt to prepare an analogous compound, 208, was considered. It was expected that 208 could be derived from 2,2-diphenyl-3-methoxy-4-methylenethietane (114) and di-

\[
\text{CH}_2=\text{C}=\text{CH-OCH}_3 + \text{S}
\]

[113]  

\[\text{hv}\]

[95]

\[\begin{array}{c}
\text{H}\\
\text{CH}_3\\
\text{S}\\
\text{CH-OCH}_3
\end{array}\]

[115]

\[\begin{array}{c}
\text{H}\\
\text{CH}_3\\
\text{S}\\
\text{CH}_2=\text{C}=\text{CH-OCH}_3
\end{array}\]

[114]

\[\begin{array}{c}
\text{CH}_3\\
\text{O}\\
\text{CH}_2\\
\text{S}
\end{array}\]

[115]

\[\begin{array}{c}
\text{CH}_3\\
\text{O}\\
\text{CH}_2\\
\text{S}
\end{array}\]

[208]

methylamine. Paquette et al. (155) had shown that dimethylamine could be added to the double bonds of 2-methylene-4-phenyl-2H-thiete 1,1-dioxide (225) to give a dimethylamino derivative 219 in 46% yield.
The synthesis of 114 was claimed by Bos and his coworkers (134a). They reported that irradiating a mixture of thiobenzophenone (95) and methoxyallene (113) for twenty minutes, under uv light generated from a mercury lamp and filtered through a potassium dichromate solution, gave a mixture of 114 and 115, both in a yield of 15-20%. Although the yield of 114 was low, a suitable quantity for generating the final product, 208, could be easily obtained by repeating the simple photochemical process. The methoxyallene (113) was a known compound (156) and was prepared, according to the procedures taken from literature, from methyl propargyl ether (217) which was obtained (157) by methylating propargyl alcohol.

Treating 217 with dimethyl sulfate in the presence of base gave 218 as a colorless liquid. The pmr spectrum of 218 showed a triplet (2.62 ppm) for one acetylenic proton, a singlet (3.33 ppm) for three methyl protons, a doublet (4.14 ppm) for two methylene protons. The doublet and the triplet resulted from a long range coupling between the acetylenic proton and the methylene protons (J=2.5 Hz). An anisotropic shielding of the triple bond caused the high field absorptions of the acetylenic proton. Treating 218 with sodium butoxide generated 113 as a colorless liquid. The pmr spectrum of 113 showed a singlet (2.93 ppm) for three methyl protons and a triplet (6.30 ppm) for one methine proton. Again, long range coup-
ling occurred between the methine and the methylene pro-
tons, $J=5.5$ Hz.

When the reaction of thiobenzophenone (95) with methoxyallene (113) was performed, results obtained were not in agreement with those claimed by Bos et al. (134a). Bos and his coworkers claimed that the reaction was photo-
chemical but the present findings proved that the reaction was thermal. When 113 and a benzene solution of 95 was mixed thoroughly under nitrogen, the blue color of 95 gradu-
dually faded and completely disappeared within 1½ hours, without requiring the irradiation procedure that Bos et al. used. To prove that the reaction was not caused by the laboratory fluorescent light, two parallel experiments were carried out simultaneously. In one experiment, the reaction of 95 and 113 was allowed to proceed in the dark while in the second experiment, the mixture of 95 and 113 was exposed to uv light filtered through a solution of po-
tassium dichromate. Both reactions were found to be com-
plete within 1½ hours, the same reaction time found from the reaction occurring under laboratory fluorescent lights. The blue color of 95 remained very intense after twenty minutes of irradiation, while Bos et al. claimed that the reaction completed after twenty minutes of irradiation. The reason for this discrepancy is not known at the present time.

Analysis by thin layer chromatography showed that the three reactions performed under different conditions
(laboratory fluorescent light; in the dark; and exposure to uv light filtered through potassium dichromate solution) resulted in the formation of the same products in about the same yields. Bos et al. (134a) reported that 114 and 115 were both formed in 15-20% yields after twenty minutes of uv exposure and probably referred to the composition of 114 and 115 in the crude reaction mixture before isolation. The reaction mixtures obtained from above three experiments performed under three different conditions were all pale yellow in colour. After exposing to the air, the colour of the solutions gradually became red, indicating the presence of certain unstable products. When the reaction mixtures were worked up, 115 was easily isolated as a pale yellow solid in a yield greater than 50% (cf. 15-20% reported by Bos et al.). The pmr spectrum of 115 showed signals compatible with those reported by Bos et al. (134a). Attempts to isolate 114 however, encountered difficulties. When a reaction mixture of 114 and 115 was eluted through a silica gel or neutral alumina columns, only unidentified degraded substances were recovered as a red mixture. It was reported that 'dry column chromatography' afforded a better efficiency of separation than liquid column chromatography, and a good resolution comparable with that of thin layer chromatography (158). When one gram of a mixture of 114 and 115 was treated twice by using 'dry column chromatography', 115 was found to be completely decomposed but a small quantity (20 mg) of grossly purified 114 was obtained. The pmr spec-
Spectrum of this sample showed signals in agreement with those presented by Bos et al. for 114. More than ten phenyl protons were found at 6.8-8.0 ppm, probably due to the presence of a compound having a structure similar to 226 which was also isolated by Bos according to a private communication (134b).

![Chemical Structure](image)

Bos et al. reported that 114 was an unstable red oil which oxidized readily in air (134b). Inspection of the structure of 114, however, indicated that the compound does not contain a highly conjugated system and should not have colour. The red colour was probably due to the contaminants derived from the decomposition of 114 and 115. Spontaneous evaporation of about 10 mg of 115 dissolved in 1 ml of chloroform, resulted in a red oil containing at least two major components which were different from 115 as revealed by tlc analysis.

The instability of 114 and the unexpected difficulty encountered in its isolation precluded the approach to synthesize 208 through 114. The work was not pursued further.
7. Chemical reactions of 2,4-diphenylthiete 1,1-dioxide and attempted synthesis of 2,4-diphenylthietan-3-one 1,1-dioxide

In connection with our interests in the chemistry and the biological activity of thietane derivatives, 2,4-diphenylthiete 1,1-dioxide (227) was submitted to various chemical reactions with the hope to produce 2,4-diphenylthietan-3-one 1,1-dioxide (228) for study as an antiinflammatory agent. The study of the chemical reactivity of 227 was considered to be interesting with respect to the susceptibility of the olefinic bond of thiete 1,1-dioxides to nucleophilic attack (84, 85), in addition to chemical rearrangement reactions (159-161) of 4-membered cyclic sulfones. It has been recently reported that 2-aryl-3-aminothiete 1,1-dioxides (229) (162, 163) and 2-phenylbenzo-(b)-thiophen-2H-3-one 1,1-dioxide (230) (164) possessed antiinflammatory activity. The structural similarity of 228 to 229 and 230 suggested that 228 may likewise prove interesting as an antiinflammatory agent. Attempts to convert 227
to 228 were thus considered to be worthwhile with respect to the pharmacological activity of the expected product and the chemical nature of the starting material.

The synthetic routes designed to generate the expected product 228 involved nucleophilic addition, hydration, hydroboration as well as hydrolysis of an enamine, 231, as shown in Scheme II.

The addition of HCN to the double bond of thiete 1,1-dioxides (232) has been reported (84, 85). It was suggested that the reaction occurred through the formation of
Scheme II

Attempted synthesis of 2,4-diphenylthietan-3-one 1,1-dioxide (228)

\[
\begin{align*}
\text{CH} &= \text{CH} - \text{N} - \text{CH}_3
\end{align*}
\]

1. \(\text{CH}_2\text{SO}_2\text{Cl}, \text{Et}_3\text{N}\)
2. Oxidative deamination

\[
\begin{align*}
\text{NaOH, H}_2\text{O} & \\
\text{or} & \\
\text{H}_2\text{SO}_4, \text{H}_2\text{O} & \\
\text{or} & \\
1. \text{B}_2\text{H}_6, 2. \text{H}_2\text{CrO}_4 & \rightarrow
\end{align*}
\]

227

232

231

228
a carbanion (233) which picked up a proton to give the product 183. It appeared that the strong electron-withdrawing sulfone group activated the double bond toward the nucleophilic addition. Other strong nucleophilic reagents such as OH\textsuperscript{−} were expected to attack the double bond in a similar manner. Treating 2,4-diphenylthiete 1,1-dioxide (227) with aqueous sodium hydroxide solution, however, resulted in the isolation of dibenzylsulfone (234). No appreciable amount of the desired product 235 was detected. It was likely that 235 was formed in the reaction but, under the basic reaction conditions, rapidly underwent ring cleavage to give 234. This type of reverse Aldol condensation has been known to occur with 2-phenylthiete 1,1-dioxide.
(236) and 2-phenyl-3-hydroxythietane 1,1-dioxide (237) which, upon heating in an aqueous sodium hydroxide solution, gave the same product, benzyl methyl sulfone (238).
It was thought that an alternate route to 228 could be achieved through the electrophilic addition of borane to 227. Olefins are well known to undergo electrophilic addition. Although the sulfone group in 227 would be expected to deactivate the double bond, the phenyl substituent attached to C-2 might lessen this effect to a certain extent by dispersing the positive charge of the transition state. The addition of borane to alkene has been known to generate a borane adduct which yields an alcohol or ketone after oxidation. Because of the electronic nature of the borane, the reaction occurs in an anti-Markownikoff manner. It was therefore expected that borane might attack C-3 of 227 and the desired product could be obtained after oxidizing the borane intermediate 240. Treating 227 stepwise with diborane and chromic acid, however, failed to give 228 and resulted only in the recovery of unchanged starting material. The resistance of 227 to borane
addition implies that deactivating effects of the sulfone group on the double bond and inductive effects of the substituent are sufficient to prevent substantial formation of the transition state 239.

That the olefinic bond of 227 was not sensitive to electrophilic addition reactions was once again demonstrated by means of treating 227 with concentrated sulfuric acid. Olefins have been known to react with concentrated sulfuric acid to form an alkyl hydrogen sulfate which can be easily hydrolyzed, with water, to an alcohol. The addition of sulfuric acid to the double bond involves the elec-
trophic attack of hydrogen, leading to the formation of a carbonium ion. The orientation of addition depends on the stability of the carbonium ion formed (i.e., benzylic carbonium > 3° carbonium > 2° carbonium > 1° carbonium ion).

\[
\text{trophilic attack of hydrogen, leading to the formation of a carbonium ion. The orientation of addition depends on the stability of the carbonium ion formed (i.e., benzylic carbonium > 3° carbonium > 2° carbonium > 1° carbonium ion).}
\]

Inspection of the possible orientation of the addition of sulfuric acid to 227 indicates two possible carbonium ions, 241 and 242. In consideration of the de-

![Diagram](image-url)
stabilization of the benzylic carbonium ion 241 by the adjacent sulfone group and steric factors involved during the subsequent nucleophilic addition of the bisulfate ion, it would appear that carbonium ion 242 would be preferred and 235 might be obtained as product.

When 227 was dissolved in cooled concentrated sulfuric acid, a brown solution was obtained. Diluting this brown solution with water resulted in isolation of two isomeric cyclic sulfinates, 3,\textsubscript{c}-5-diphenyl-1,\textsubscript{r}-2-oxathiacyclopenta-3-ene 2-oxide (243) and 3,\textsubscript{t}-5-diphenyl-1,\textsubscript{r}-2-oxathiacyclopenta-3-ene 2-oxide (244), as a 3:2 (243:244) mixture.
None of the desired product 235 was detected.

Cyclic sulfinates (sultines (161)) are rare compounds and only ten sultines had been reported in the literature at the time when the present work was performed; five (245-249) via thermal isomerization of thietane 1,1-dioxides at 300-400° (159, 160, 165, 161), one (250) by synthesis through chlorine oxidation of benzothiadiazine
(161), two (251, 252) by the action of t-butoxymagnesium bromide on 2,4-diphenylthietane 1,1-dioxides (159, 166) and two unsubstituted four- and five-membered sultines (255 and 256) via desulfurization of thiosulfonates (253, 254) by aminophosphine (257) (167). More recently, several un-

\[
(CH_2)_nS=S\stackrel{\text{O}}{\text{O}} + P(\text{NET}_2)_3 \rightarrow (CH_2)_nS\text{O} + P(\text{NET}_2)_3
\]

\[
\begin{align*}
253 & \quad n=1 \\
254 & \quad n=2 \\
255 & \quad n=1 \\
256 & \quad n=2
\end{align*}
\]

stable four-membered sultines (259) were claimed (168) to be the intermediates in the formation of olefins (260) from \(\beta\)-hydroxy sulfoxide (258), an analogous reaction of
the Wittig olefin synthesis. These four-membered sultines were found to have only limited thermal stability. They readily lost \( \text{SO}_2 \) within a few minutes at room temperature to give olefins. Sultine 261 was found to be relatively stable and was the only sultine for which the pmr data was
provided. During the last two years, only one more sultine (262) was added to the literature (169).

![Chemical structure of sultine 262](image)

The conversion of unsaturated four-membered cyclic sulfones to their corresponding $\gamma$-sultines was reported only from two laboratories (159-161, 165). Dittmer et al. (160) reported the isolation of sultine 248 upon pyrolysis of a naphthothiete sulfone (263) in the presence of 9,10-dihydroanthracene. The pyrolysis of 263 without using 9,10-dihydroanthracene was found to take a complete different reaction course and give different products. The au-
The authors suggested that the pyrolysis of thiete sulfone involves initial scission of the sulfur-carbon bond to give a diradical intermediate which cyclizes to yield sulfinate by formation of an O-C bond. The role of dihydroanthracene in the reaction was uncertain. The authors suggested that it interacted with the intermediates formed or with sultine to prevent extensive rearrangement.

Thermolysis of thiete 1,1-dioxide and 2-phenylthiete 1,1-dioxide gave the corresponding 5H-1,2-oxathiolene 2-oxides (161). The reaction
was also explained in terms of the formation of sulfene (266) by electrocyclic opening of the thiete ring.

The rearrangement of a 4-membered cyclic sulfone to sultine by using chemical reagents has been described from only one laboratory (159, 165). Dodson et al. (159) reported that treating 2,4-diphenylthietane 1,1-dioxides (266) with t-butoxymagnesium bromide gave 3,5-diphenyl-1,2-oxathiolane 2-oxides (267). The rearrangement was sug-

![Chemical structure](image)

gested to be catalyzed by base and an ionic mechanism was proposed as described in the following scheme:
The constitution of sultines 243 and 244 was established as follows: Elemental analysis proved the molecular formula to be C_{15}H_{12}O_2S. Mass spectrum displayed an intense peak (m/e 208) attributed to (M^+ - SO), in agreement with the finding of Dittmer et al. (160) that a (M^+ - SO) peak was observed in the mass spectrum of 248. The ir spectra of 243 and 244 showed the absence of sulfone and the presence of a sulfinate band (160, 168, 170) at 1125 cm\(^{-1}\). The pmr spectra of 243 and 244 confirmed their structures. The chemical shifts (243: 6.73 ppm; 244: 6.80 ppm) of the olefinic protons (H\(_b\)) agreed with the values of 6.70 and 6.81 ppm for the corresponding olefinic protons in 245 and 246 (Table V). The pronounced difference (0.51 ppm) in the chemical shift values of proton H\(_a\) in 243 (6.39 ppm) and that in 244 (6.90 ppm) is in accordance with the observation (159, 160, 161, 171) that the sulfinyl bond (S=O)
caused a downfield shift to those protons which were cis to the sulfinyl bond. This effect is illustrated by the \( \delta \)-values of proton \( H_b \) in compounds 245-248 (Table V).

Larger \( \delta \)-values for proton \( H_a \) in sultines 243 (6.39 ppm) and 244 (6.90 ppm) as compared to the parent sulfone 227 (5.92 ppm) indicate that the benzylic proton in 243 and 244 is indeed contained in a \(-S-O-CH-\) structural configuration. The other possible positional isomers containing the configuration \(-O-S-CH-\) as in 268 would be expected to display the benzylic proton at lower \( \delta \) values.

Protons vicinal to a sulfone group are shielded less than if adjacent to a sulfinate group. For instance the two me-
Table V

Chemical Shifts of sultines

<table>
<thead>
<tr>
<th></th>
<th>Ha</th>
<th>Hb</th>
<th>Hc</th>
<th>Hd</th>
</tr>
</thead>
<tbody>
<tr>
<td>245 (161)</td>
<td>5.06</td>
<td>5.41</td>
<td>6.70</td>
<td>6.90</td>
</tr>
<tr>
<td>246 (161)</td>
<td>5.32</td>
<td>5.72</td>
<td>6.81</td>
<td>-</td>
</tr>
<tr>
<td>248 (160)</td>
<td>5.31</td>
<td>5.98</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>249 (161)</td>
<td>5.42</td>
<td>5.78</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
ethylene protons in sulfinate 261 (168) possess a smaller δ-value than the corresponding α-methylene protons in sulfone 269 (171-173). The C-3 proton in sultines 251 and 252

261

Hα = 3.7 ppm(m)
Hβ = 5.3 ppm(m)

269

Hα = 4.34 ppm(m)

has a smaller δ-value than the Hα proton in thietanes 270 and 271 whereas the C-5 proton in 251 and 252 has a larger δ-value than the Hα proton in 270 and 271 (159, 174). The sulfinyl oxygen in sultines 243 and 244 was considered to most likely assume an equatorial orientation since a 1,3-diaxial interaction would be expected to occur between an axial sulfinyl oxygen and the C-5 axial group.
The reaction of concentrated sulfuric acid with 2,4-diphenylthiete 1,1-dioxide may be rationalized in terms of initial scission of the sulfur-carbon bond to generate a benzylic carbonium ion which then gives sultines 243 and 244 by formation of an oxygen-carbon bond. The formation...
of a benzylic carbonium ion intermediate was supported by the fact that the reaction did not occur with 2-phenylthiete 1,1-dioxide (272) and 2-phenyl-4-methylthiete 1,1-dioxide (273). The primary and secondary carbonium ions derived from 272 and 273 respectively would not be expected to be as stable as the benzylic carbonium ion generated from 227.

![Chemical Structures]

Rosen (175) and Truce et al. (176) reported that 3-aminothiete 1,1-dioxides (274, 275, 277, 278) were converted into their corresponding ketones (276) or enols (279) upon reaction with hydrochloric acid or treatment with an ion-exchange resin. It was felt that this reaction would be a facile route for preparation of 2,4-diphenyl-...
thietan-3-one 1,1-dioxide (228) from a known enamine, 2,4-diphenyl-3-diethylaminothiete 1,1-dioxide (231). The thiete could be synthesized by the reaction of benzylsulfonyl chloride (60) and N,N-diethylphenylethynylamine (285) derived from phenylacetyl chloride (281) (177-179). The preparation of ynamine 285 was straight forward, according to
published methods (178, 179), and its structure was confirmed by spectroscopic data which had not previously been reported. The ir spectrum displayed a characteristic acetylene peak at 2210 cm$^{-1}$. The pmr spectrum showed a triplet (1.16 ppm) for six methyl protons, a quartet (2.82 ppm) for four methylene protons and a multiplet (6.98-7.45 ppm) for five phenyl protons. The cycloaddition reaction of ynamines with sulfonyl chlorides has been extensively reviewed (102-107). In the presence of triethylamine, sulfene 286 is generated and attacks the ynamine through an initial Zwitter-ion 287 which undergoes intramolecular cyclization to yield 2,4-diphenyl-3-diethylaminothiete 1,1-dioxide (231). The structure of 231 was confirmed by the spectroscopic data. The ir spectrum showed characteristic absorptions of sul-
fome (1165 and 1300 cm$^{-1}$) and enamine (1625 cm$^{-1}$). The pmr spectrum displayed a triplet (0.85 ppm) and a quartet (3.03 ppm) for six methyl and four methylene protons respectively, a singlet (5.73 ppm) for one benzylic proton and a multiplet (7.15-7.65 ppm) for ten phenyl protons.

When enamine 231 was treated with ion-exchange resins (BIO-RAD AG50W-X8 and Amberlite 120) according to Rosen's method for conversion of 3-aminothiete 1,1-dioxides (274, 275) to the corresponding thietan-3-one 1,1-dioxide (276), unchanged starting material (231) was recovered. In concentrated hydrochloric acid, 231 was also found resistant to expected hydrolysis. Truce et al. (176) reported that 2-phenyl-3-diethylamino-4-methylthiete 1,1-dioxide (277) was stable in dilute aqueous HCl, but in benzene solution and in the presence of trace hydrochloric acid, was readily transformed into 2-phenyl-3-hydroxy-4-methylthiete 1,1-dioxide (279). Treating an acetone solution of 231 with concentrated hydrochloric acid for one week or refluxing a solution of 231 in a HCl-acetone mixture for three hours,
also resulted in recovery of the unchanged starting material, 231.

Inspection of the structure of 231 showed that the molecule contains a highly conjugated system. The resonance stabilization as described by 288 may account for the resistance of 231 to acid hydrolysis. Further efforts to hydrolyze 231 were abandoned and the attempted synthesis of 228 was not continued at this time.
2,2-Diphenyl-3-dimethylaminomethylthietane 1,1-dioxide (32), cis-2,2-diphenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide (33), and trans-2,2-diphenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide (34) were tested for their analgesic activity. The method used was similar to that described by Cox and Weinstock (56) and was based on the ability of narcotic analgesics to produce a block of contractions of the electrically stimulated ileum. Male guinea pigs (300-500 gm) were starved overnight and killed by a blow on their heads. The ileum was immediately isolated and kept in Krebs solution at 37°, oxygenated with 95% O₂ and 5% CO₂. A length of ileum (2-3 cm) was removed and set up in a 15-ml organ bath containing oxygenated Krebs solution at 37°. The lower end of the gut was threaded to a glass anchor positioned at the bottom of the organ bath. The upper end of the gut was tied to a lever which recorded
the gut movements on a kymograph. Both ends of the ileum were left open. The tension (about 2-3 gm) on the gut was adjusted so that a level baseline was obtained. Two platinum stimulating electrodes were used, one being inserted into the intraluminal space and the other being placed in the bath solution. The tissue was stimulated by single square wave pulses (0.5 msec) delivered every 7 seconds from a Grass SD9 stimulator. The voltage was adjusted initially to give about 80% maximum response (30-35 volts). The tested compounds were dissolved in ethanol and were added in a volume of 0.025 ml. Methadone hydrochloride which was used as a reference narcotic was dissolved in water and added in a volume of 0.1 ml. Naloxone hydrochloride, a narcotic antagonist, was also dissolved in water and added in a volume of 0.1 ml. The drugs were left in contact with the tissue for 2-5 min. and after washing out, the ileum was allowed to return to its control height before the next dose or next drug was added.

Ethanol was used as solvent for the test compounds because of the solubility problem. At a volume of 0.025 ml ethanol did not produce any detectable depression on the electrically induced gut contractions. The depression by methadone of the gut contractions was not affected by the presence of 0.025 ml of ethanol as well. A solution of methadone hydrochloride in ethanol (1.1 x 10^{-8} M) produced the same percentage of depression as an aqueous
solution of methadone hydrochloride and the depression was effectively reversed by naloxone hydrochloride $(2 \times 10^{-8} \text{ M})$.

Methadone hydrochloride was found to depress the electrically induced contractions of ileum by 44% and 83% at concentrations of $1.1 \times 10^{-8}$ M and $1.1 \times 10^{-7}$ M respectively. The depressions were immediately reversed by the addition of naloxone hydrochloride at a concentration of $2 \times 10^{-8}$ M (Fig. IV).

The ability of three tested compounds to depress the response of ileum to electrical stimulation is shown in Figures III and IV. It is obvious that the compounds block the contractions at concentrations much higher than those of methadone. At these high concentrations the compounds are believed to act by nonspecific mechanisms.

To determine whether or not the block of contractions by the tested compounds was a real narcotic effect, naloxone hydrochloride $(2 \times 10^{-8} \text{ M})$ was added to the organ bath after the gut contractions had been depressed by the compounds $(3.3 \times 10^{-5} \text{ M})$. It was observed that naloxone was incapable of reversing the depressive action of all three compounds. This result shows that the compounds inhibited the electrical contractions by a mechanism different from that of the blockade induced by narcotic analgesics such as morphine and methadone etc. indicating that the compounds are devoid of narcotic
analgesic activity.

In order to determine whether the compounds possessed narcotic antagonistic activity, the ileum was treated with methadone hydrochloride \((1.1 \times 10^{-7} \text{ M}, 2\) minutes), followed by the tested compound at a concentration of \(3 \times 10^{-7} \text{ M}\). The inhibitory action of methadone was found not to be reversed by the compounds but immediately antagonized by a subsequent dose of naloxone hydrochloride \((2 \times 10^{-8} \text{ M})\). In an alternate procedure the ileum was pretreated with the tested compound \((3 \times 10^{-7} \text{ M})\) followed by methadone \((1.1 \times 10^{-7})\). None of the tested compounds prevented or reduced the blocking action of methadone on the ileum contractions.

In addition to the guinea-pig ileum test, the absence of significant activity of three tested compounds was further supported by the result obtained from determination of the pain threshold of one rabbit to the electrical stimulation in its tooth-pulp. The animal and the set-up were kindly supplied by Dr. John G. Sinclair, Faculty of Pharmaceutical Sciences, The University of B.C., and the test was performed by Mrs. Majorie F. Chaplin. The tested compounds were dissolved in ethanol and injected into the lateral ventricle \((180)\) of the rabbit \((2.3 \text{ Kg})\). The tooth-pulp of the animal was stimulated by single pulses \((10 \text{ msec, } 3 \text{ Hz})\) delivered from a Grass S8 stimulator. The voltage at
which the animal licked its lips or chewed its teeth was considered as threshold voltage. The threshold voltage of the tested rabbit given either artificial C. S. F. or 0.05 ml of ethanol intraventricularly was 13-13.5 V. At a dose of 300 μg (in 0.05 ml of ethanolic solution), compounds 32, 33 and 34 did not significantly change the threshold voltage which was observed every 5 minutes for 30 minutes after administration of the drugs. Observation was extended to 75 minutes for compound 34 and no analgesic activity was detected. Compound 33 given at double dose (600 μg, 0.1 ml) also produce no analgesic activity. Morphine sulfate at dose of 50 μg raised the pain threshold to 30 V at 15 minutes after intraventricular administration.
Inhibition of contractions of electrically stimulated guinea-pig ileum by methadone (●), compounds 32 (×), 33 (○) and 34 (▽). Each point represents the average of two determinations on two ileum preparations.

% Inhibition

Molar concentrations of test compounds
Figure IV

Effect of methadone, thietane 1,1-dioxides and naloxone (2 x 10^{-8} M) on guinea-pig ileum contractions.

Methadone, 1.1 x 10^{-8} M

Naloxone

Methadone 1.1 x 10^{-7} M

Naloxone

Compound 22, 3.3 x 10^{-5} M

Naloxone

Wash

Compound 22, 3.3 x 10^{-5} M

Naloxone

Wash

Compound 24, 3.3 x 10^{-5} M

Naloxone

Wash
PARTITION STUDIES

It is expected that narcotic drug molecules travel through many membrane barriers before they reach their locus of action. The relationships between the analgesic activity of narcotics and their partition coefficients (P) have been well documented: Casy and Wright (181) have related the high analgesic potency of benzimidazole derivatives to their higher partition coefficients than that of morphine. In the work of Kutter et al. (182) the analgesic potency of morphine and related synthetic analgesics have been shown to depend partly on their log P values. The high analgesic activity of nonpolar narcotics following intravenous administration was explained by a good penetration of these compounds through the blood brain barrier. The analgesic potency of etorphine (3800 times the activity of dihydromorphine after intravenous injection) has been considered to arise in large part from its high lipophilicity (183). In an in vitro study of binding of narcotic analgesics to cerebroside sulfate, the binding was shown to correlate with the heptane solubility of the compounds (184).

It was of interest to see if thietane compounds had any unusual partition properties that may account for the results of the analgesic tests. Compounds with restricted conformation have been known to have dissimilar lipophilicities as compared to the extended analogs.
The present study was undertaken with a view to making a preliminary assessment of the physico-chemical influence of the thietanes on their analgesic activity by using a simple partition method. Direct determination of partition coefficients of compounds 32-34 presented practical difficulties because limited quantities of the test compounds were available and the compounds were poorly soluble in either water or nonpolar phases such as 1-octanol, paraffin, heptane and corn oil. The problem of measuring low concentrations of solute by specific quantitative analytical methods was also foreseen. The reversed-phase thin layer chromatography method was thus chosen to compare the lipophilicity of the compounds to that of methadone. This method was based on the theoretical relationship between the partition coefficient and the \( R_f \) value deduced by Martin (186):

\[
P = K \left( \frac{1}{R_f} - 1 \right)
\]

Where \( K \) is the constant for the system. Bate-Smith and Westall (187) introduced the term \( R_m \), where \( R_m = \log \left( \frac{1}{R_f} - 1 \right) \). It is therefore possible in principle to correlate the lipophilic property of substances with their \( R_m \) values (equation 2). The validity of this theory has been established by a number of workers (188-191). The partition coefficients determined with different solvent systems for twelve narcotic analgesics extending from the hydrophilic N-methylmorphine to the lipophilic metha-
done has been shown parallel to the $R_F$ values determined by thin layer chromatography (26). In a series of para-substituted acetanilides, the analgesic activity was shown to correlate better with the chromatographic substituent constant $\Delta R_m$ than with Hansch's hydrophobic substituent constant $\alpha$ derived from the partition coefficient. It was also observed that better correlation of $\Delta R_m$ and analgesic activity was obtained when the lipophilic phase was 1-octanol than when it was liquid paraffin (189).

The procedure used was in general similar to that described by Biagi et al. (192). Chromatography was carried out on commercially available cellulose sheets which were impregnated with 1-octanol by dipping into a solution of 5% 1-octanol in hexane. The mobile phase was a solution of 0-20% (v/v) methyl ethyl ketone in water. The chromatogram was visualized by spraying with Dragendorff reagent plus 0.01 N sulfuric acid if necessary. The $R_F$ values of the pink spots that appeared were measured and transformed into $R_m$ values which were plotted against the ketone concentrations in the mobile phase. The $R_m$ values at 0% ketone (Table VI) were calculated by extrapolation from the regression lines. The $R_F$ values characterize the migration of the compounds with the polar phase. The greater the $R_F$ values, the smaller the $R_m$ values and the more hydrophilic the compounds appear to be.

Table VI shows the calculated $R_m$ values for
Table VI

Rm values at 0% methyl ethyl ketone calculated from regression lines

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rm (l-octanol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃)₂NCH₂HCl (\text{SO}_2) (\text{C}_6\text{H}_5)</td>
<td>289 1.70</td>
</tr>
<tr>
<td>(CH₃)₂NCH₂H (\text{C}_6\text{H}_5) (\text{SO}_2)</td>
<td>34 1.43</td>
</tr>
<tr>
<td>(CH₃)₂NCH₂H (\text{C}_6\text{H}_5) (\text{SO}_2)</td>
<td>33 1.32</td>
</tr>
<tr>
<td>Methadone (\text{CH}_3)</td>
<td>0.89</td>
</tr>
<tr>
<td>(CH₃)₂NCH₂H (\text{C}_6\text{H}_5) (\text{SO}_2)</td>
<td>290 0.70</td>
</tr>
</tbody>
</table>
compounds 289 and 290 as well as methadone as reference. Compound 290 has a smaller $R_m$ value (less lipophilic) than methadone as expected, probably due to the fact that the former compound lacks a lipophilic C-2-phenyl substituent and has a sulfonyl group which in nature is more hydrophilic than the carbonyl function (193). The higher lipophilicity of compounds 33, 34 and 289 than methadone suggests that the two C-2-phenyl substituents exert significant steric effects on the hydrophilic nature of the sulfonyl group. The shielding of the lone pair electrons of two sulfonyl oxygen atoms is expected to produce significant increases in $R_m$ values (185). In 289 the presence of a lipophilic chlorine substituent also contributes to the largest $R_m$ value (193).

In Table VII are presented the log P and $R_m$ values for a number of narcotic agonists and antagonists calculated from the partition coefficient data (1-octanol-water system, pH = 7.4, 20°C) determined by Kaufman et al. (183) and the $R_f$ values determined from a similar reversed-phase partition chromatographic method (mobile phase: water containing 10% ammonium formate, stationary phase: paper impregnated with 20% 2-octanol in acetone) by Genest and Farmilo (194). Comparison of the $R_m$ data shown in Table VII with those of thieterane 1,1-dioxides determined in the present study (Table VI) suggests that the lipophilicities of the thieterane 1,1-dioxides 33, 34 and 289 lie
Table VII

Log P(1-octanol) and Rm(2-octanol) values of narcotic agonists and antagonists calculated from literature data (183, 194)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Log P(1-octanol)</th>
<th>Rm(2-octanol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxymorphone</td>
<td>-0.33</td>
<td>-0.60</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.07</td>
<td>0.55</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.23</td>
<td>-0.58</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>0.63</td>
<td>-</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>0.64</td>
<td>-</td>
</tr>
<tr>
<td>Cyclazocine</td>
<td>0.89</td>
<td>-</td>
</tr>
<tr>
<td>Naloxone</td>
<td>1.12</td>
<td>-</td>
</tr>
<tr>
<td>Nalorphine</td>
<td>1.27</td>
<td>-</td>
</tr>
<tr>
<td>Meperidine</td>
<td>1.37</td>
<td>-0.18</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>1.60</td>
<td>-</td>
</tr>
<tr>
<td>Methadone</td>
<td>1.64</td>
<td>+0.43</td>
</tr>
<tr>
<td>MR1256BS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.13</td>
<td>-</td>
</tr>
<tr>
<td>MR1029BS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.56</td>
<td>-</td>
</tr>
<tr>
<td>α-Acetylmethadol</td>
<td>2.69</td>
<td>+1.28</td>
</tr>
<tr>
<td>Myrophine</td>
<td>-</td>
<td>+2.00</td>
</tr>
</tbody>
</table>

a Logarithms of partition coefficients determined by Kaufman et al. (183) (1-octanol-water system at 20° pH = 7.4)

b Rm values calculated from Rf data determined by Genest and Farmilo (194) (mobile phase: water containing 10% ammonium formate; stationary phase: paper impregnated with 2-octanol)

c Pure narcotic antagonist (183)

d Mixed narcotic agonist-antagonist
between those of methadone and myrophine which is a potent
narcotic analgesic. Theoretical mathematic transformation
of the \( R_m(2\text{-octanol}) \) value of myrophine (Table VI) into the
\( R_m(1\text{-octanol}) \) value of the partition system used in the
present study gives a \( R_m(1\text{-octanol}) \) value equal or larger
than 2.15*, indicating that the lipid solubility of myro-

* A linear relationship between the \( R_m \) values found in
one solvent system and those found in a second can be
derived from Hansch's (185) solvent regression equa-
tion (equation 3) and equation 2 where \( a, b \) and \( c \) are

\[
\log P(\text{solvent}) = a \log P(1\text{-octanol}) + b \quad (\text{equation 3})
\]

\[
R_m(\text{solvent}) = a R_m(1\text{-octanol}) + c \quad (\text{equation 4})
\]

constants. In Hansch's excellent review of partition
coefficients (185) the constant \( a \) has been shown to be
a measure of a solvent system's sensitivity to changes
in the lipophilicity of solute. In a number of alcohol-
solvent systems, the constant \( a \) varies from 0.695 to
1.00. A maximum sensitivity is reached at 1-octanol and
oleyl alcohol with constant \( a \) being 1. Substituting in-
to equation 4 the known terms: \( a = 0.695 \) to 1.00;
\( R_m(\text{solvent}) = R_m(2\text{-octanol}) = 0.432 \) for methadone found
in the reversed-phase partition system of Genest and
Farmilo (Table VII) and \( R_m(1\text{-octanol}) = 0.89 \) for metha-
done found in the present study (Table VI), the const-
ant \( c \) is calculated to be in the range between -0.146
and -0.458. Substituting \( R_m(\text{solvent}) = 2.00 \) for myro-
phine (Table VII) into equation 4 results \( R_m(1\text{-octanol}) \)
\( \geq 2.15 \).
phine is higher than that of thietane 1,1-dioxides (Table VIII). The calculation of log $P_{(1-octanol)}$ values of thietane 1,1-dioxides 33, 34, 289 and 290 by using equation 2* also gives figures indicating that the lipophilicities of 33, 34 and 289 (Table VIII) lie between those of methadone and $\alpha$-acetylmethadol which is a potent and long acting narcotic analgesic. It follows therefore that the lack of analgesic activity in compounds 32-34 does not appear to rest with the nature of their lipophilicity. The choice of an in vitro guinea-pig ileum method to test the compounds excludes many effects of absorption and distribution on the results. In the rabbit tooth pulp test the intraventricular administration of compounds also circumvents many penetration factors.

* $k$ is calculated by using methadone as a standard:

$$\log P_{(1-octanol)} = 1.635 \text{ and } R_m(1-octanol) = 0.43$$

(Table VII).
Table VIII
Comparison of calculated $R_m$ (1-octanol) and log $P$ (1-octanol) values of thietane 1,1-dioxides with literature data of narcotic agonists and antagonists (183, 194)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>$R_m$ (1-octanol)$^c$</th>
<th>log $P$ (1-octanol)$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>290</td>
<td>0.70</td>
<td>1.45$^d$</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.89</td>
<td>1.64</td>
</tr>
<tr>
<td>33</td>
<td>1.32</td>
<td>2.07$^d$</td>
</tr>
<tr>
<td>MRL1256BS$^a$</td>
<td>-</td>
<td>2.13</td>
</tr>
<tr>
<td>34</td>
<td>1.34</td>
<td>2.18$^d$</td>
</tr>
<tr>
<td>289</td>
<td>1.70</td>
<td>2.45$^d$</td>
</tr>
<tr>
<td>MRL1029BS$^b$</td>
<td>-</td>
<td>2.56</td>
</tr>
<tr>
<td>$\alpha$-Acetylmethadol</td>
<td>-</td>
<td>2.69</td>
</tr>
<tr>
<td>Myrophine</td>
<td>2.15$^d$</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Pure narcotic antagonist (183)
$^b$ Mixed narcotic agonist-antagonist (183)
$^c$ Experimental data determined from present partition study
$^d$ Calculated values. See text
$^e$ Logarithms of partition coefficients determined by Kaufman et al. (183) (1-octanol-water system at $20^\circ$, pH = 7.4)
In two previous studies (84a, 85a) of narcotic analgesic activity of thietane 1,1-dioxides (27-31) containing a single phenyl ring at C-2, the lack of activity of the tested compounds was attributed to improper orientation of the equatorial phenyl ring. In 2,4-diphenylthietane 1,1-dioxides (27-29), the equatorial phenyl ring at C-4 was thought (84a) to interfere with the effective binding of the compounds at the analgesic receptor. In the present study, the fact that 2,2-diphenylthietane 1,1-dioxides 32-34 containing both equatorial and axial phenyl rings at C-2 lacked significant analgesic activity indicates that the inactivity of thietane 1,1-dioxides in the two previous studies was not mainly due to the equatorial phenyl ring. Other critical stereochemical features had to play an important role. For instance, the restricted bulky sulfone group may interfere with the receptor binding, the dimethylaminomethyl group may not assume the proper orientation to interact with the anionic site of the analgesic receptor surface, or even the C-4 and the substituent attached to it may not be compatible with the stereochemically demanding opiate receptor.

The lack of analgesic activity in compounds 32-34 supports the theory that methadone and its sulfone analogue assume a certain pharmacophoric conformation at the recep-
tor level. The flexible open chain appears to be necessary to render the methadone molecule enough freedom to adopt a conformation so that the aromatic rings, the amino group, and the remaining part of the molecule can be placed precisely on the topographical receptor sites. Restriction of the flexibility of the molecule so that the pharmacophoric conformation can no longer be achieved may thus lead to the complete loss of narcotic analgesic activity. The piperidine analogue (25) of methadone, in which the C-2 and the nitrogen atom of methadone were joined together with deprivation of one N-methyl group did not show analgesic activity (195) although its structure appears to be generally close to the proposed cyclic structure of methadone (22) (Page 10). The explanation may be that the orientation of the restricted propionyl component in 25 may not indeed mirror that of the corresponding part in the pharmacophoric conformation of methadone and thus result in hindering receptor binding. Res-
triction of the rotational freedom of the two aromatic rings has led to several methadone analogues (24, 291-295) with diminished or insignificant analgesic activity (82). It was concluded that the phenyl rings in these compounds failed to maintain the required conformation for receptor binding.

In compound 33 and most likely in 32 and 34 as well, the dimethylaminomethyl substituent possesses an equatorial orientation as represented by 296. Examination of the Newman projection of the staggered conforma-
tion of 296 about the C3-CH$_2$N bond shows that the dimethylamino group most likely adopts a synclinal relationship with respect to C-4 as represented by 297. The staggered conformation of 296 about C2-C3 bond as represented by 298 shows that the torsion angle is less than $60^\circ$ and the dimethylaminomethyl group adopts a pseudo-antiperiplanar relationship with respect to the sulfone group. The orientation of the two phenyl rings and the amino group in conformations represented by 297 and 298 do not appear to show
similar spacial arrangements to that of the corresponding groups in the pharmacophoric conformation proposed by Portoghese and his coworkers for methadone (75, 78). In

![Chemical structure](image)

the dimethylamino group and the C-4 group were described to assume a synclinal relationship as represented by while the dimethylaminomethyl group and one of the two phenyl rings assume an antiperiplanar orientation (301).
A folded conformation of 296 as represented by 302 and 303 in which the dimethylamino group is placed on top of the thietane ring, a favorable conformation to the interaction between the sulfonyl and the amino groups, seems highly unlikely because of too many nonbonded inter-

![Chemical Structure]

actions. Nevertheless the two phenyl rings in 302 and 303 do not appear to have the same orientation as that in 300 and 301. The CH₃CHSO₂ component of the thietane ring in 302 and 303 may even hinder the binding of these conformers to the narcotic receptor. Thus the change of spacial disposition of the phenyl rings and the amino group in 296 as compared to 299 may account for the lack of analgesic activity in compounds 32-34. The present result and the previous studies (82, 195) of rigid analogues of methadone such as 25 indeed reflect the exacting requirement for binding of methadone to the narcotic receptor. A small change in the conformation of methadone thus results in complete loss
of narcotic analgesic activity.
ANALYTICAL METHODS

Melting points were determined using a Thomas-Hoover Capillary Melting Point Apparatus. All melting points are reported uncorrected.

Ultraviolet spectra were obtained using a Bausch and Lomb Model 505 recording spectrophotometer.

A Beckman IR-10 infrared spectrophotometer was used to record the infrared spectra.

The pmr spectroscopy was performed by the Department of Chemistry, U. B. C., using a Varian A-60, T-60 or XL-100 spectrometer. The concentration of solutions was ca. 10% and tetramethylsilane served as the internal standard. Solvents are specified. Peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

Mass spectra and gc/mass spectral data were obtained using a Varian MAT-111 mass spectrophotometer.

Gas-liquid chromatography (glc) was carried out using a MicroTek gas chromatograph Model MT-200 equipped with a flame ionization detector and a Disc Integrator Model 222. The carrier gas was nitrogen. All other conditions and column types are specified.

Microanalyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, Fritz-Pregl-Strasse 14-16, West Germany.
EXPERIMENTAL

1. **Synthesis of thiobenzophenone (95).**

   Thiobenzophenone was prepared according to a method taken from the literature (141) with modifications. Into a stirred and cooled (ice-salt bath) solution of benzophenone (25 gm, 0.14 mole) in 125 ml of 95% ethanol, hydrogen sulfide and hydrogen chloride were simultaneously passed. After 3 hours the hydrogen chloride was disconnected. The blue solution was stirred in the ice-salt bath for a further 24 hours under a stream of hydrogen sulfide. The blue product was filtered through a Buchner funnel surrounded with dry ice, washed twice with 30 ml of cooled 95% ethanol and immediately recrystallized from n-pentane in a glove box under nitrogen. Thiobenzophenone was obtained as blue needle-like crystals (19 gm, 73%), mp 54° (lit. (141) 53-54°, 66-77%).

2. **Synthesis of 2,2-diphenyl-3-cyanothietane (155).**

   2,2-Diphenyl-3-cyanothietane was prepared by photocycloaddition of thiobenzophenone (95) to propenenitrile (144) at 366 nm (138). In a nitrogen glove box freshly recrystallized 95 (21.2 gm, 0.106 mole) and redistilled 144 (160 gm, 3.01 mole) were dissolved in a sufficient amount of redistilled cyclohexane to a volume of one liter. The bright blue solution was divided and transferred into 50-ml pyrex tubes. Five tubes were used
at one time and mounted directly in front of a filter window (Corning CS7-60 glass filter, 4.5 x 165 x 165 mm). The solutions and the window were air-cooled with two jets of compressed air. About two inches behind the filter was a medium-pressure mercury arc (Hanovia 679A36, 450 W) placed in a water-cooled quartz vessel. The apparatus was entirely enclosed in a dark hood and exposed only to the light through the window. Irradiation was performed until the blue color of the solution completely disappeared (about 4 days) and a pale yellow solution was obtained.

After irradiation the content of each tube was filtered and evaporated to a viscous liquid (1.34 gm). Purification of this crude material by column chromatography (silica gel, 48 ml in 50-ml buret; benzene/petroleum ether 30-60°, 5:3) gave a white solid (155) (0.61 gm, 41%). Recrystallization of this solid from a mixture of n-pentane and ether yielded a colorless crystalline substance (155) (0.4 gm, 31%), mp 84-85.5° (lit. (138) 84°, 93%); ir (KBr) 708, 752, 775, 1400, 1478 (phenyl) and 2234 (nitrile) cm⁻¹; pmr (CDCl₃) δ 3.40 (m, 2, SCh₂), 4.99 (t, 1, CNCH, splitting = 9 Hz) and 7.10-7.70 (m, 10, phenyl) ppm.

Attempts to improve the yield of the product were unsuccessful. Repeating the experiment by using purified propenenitrile *, replacing cyclohexane with anhydrous ether or employing combined filters (Corning CS7-60 and
CS52) did not significantly improve the yield. It was observed that using aged solutions of 95 or prolonged irradiation usually resulted in a poor yield.

3. Synthesis of 2,2-diphenyl-3-cyanothietane 1,1-dioxide (160).

To a stirred and cooled solution of 2,2-diphenyl-3-cyanothietane (155) (3.0 gm, 0.012 mole) in chloroform (50 ml) was added a solution of m-chloroperoxybenzoic acid (85%, 5.0 gm, 0.024 mole) in 100 ml of chloroform at such a speed that the temperature of the thietane solution was maintained at 15-20°. After the addition of the peracid, the resulting solution was stirred at room temperature for 1 day. One hundred milliliters of anhydrous ether was added to dissolve the precipitate that separated and the stirring was continued for 4 more days. Cautious concentration of the solution at room temperature to about 80 ml resulted in the formation of a white precipitate which was collected by filtration and was treated after the work-up of the filtrate. The filtrate was washed successively with 20% sodium sulfite solution, saturated sodium carbonate and saturated sodium chloride solutions, dried

* Propenenitrile was washed successively with 10% sulfuric acid, 10% sodium carbonate solution and a saturated solution of sodium sulfate. After drying over calcium chloride it was distilled at atmospheric pressure and finally distilled at room temperature in vacuo.
(anhydrous sodium sulfate) and evaporated to give the crude 160 as a white powder (2.62 gm), mp 129-143°.

The precipitate previously obtained was stirred in 50 ml of saturated sodium carbonate solution. Fifty milliliters of chloroform was added to dissolve the insoluble substance. The chloroform solution was separated, washed, dried and evaporated as above to give more white solid product (0.3 gm) mp 155-160°. The isolated product was combined (2.92 gm, 86%) and recrystallized once from a mixture of chloroform and ether to yield a colorless crystalline substance (160) (2.3 gm, 70%) mp 156.5-160° (lit. (138) 157-158.5°); ir (KBr) 540, 710, 788, 1450, 1498, 3040, 3065 (phenyl), 1143, 1172, 1325 (SO₂(172)) and 2265 (nitrile) cm⁻¹; pmr (CDCl₃) 84.63 (m, 3, CNCH and SCH₂) and 7.43 (m, 10, phenyl) ppm.

Using peracetic acid in place of m-chloroperoxybenzoic acid in a similar experiment resulted in a lower yield (67%) of crude 160.

4. Synthesis of 2,2-diphenyl-3-aminomethylthietane 1,1-dioxide (161).

The reaction was performed in a 250-ml three-necked flask which was equipped with a magnetic stirrer and a sintered glass dispersion tube connected to a diborane generation apparatus. The outlet of the three-necked flask was connected to an inactivation trap. The
inactivation trap was a mercury bubbler in which some mercury was laid at the bottom. Above the mercury was a layer of acetone which served to destroy the diborane escaping from the reaction flask. The diborane generator was a dry 500-ml three necked flask equipped with a magnetic stirrer, a pressure-equalizing addition funnel and a diborane outlet which was connected to a dry trap (serving as a reservoir in case of back flow of the solution from the reaction flask to the generator) and then to the gas dispersion tube dipped in the reaction flask. The top of the addition funnel served as an inlet for the dried nitrogen.

Under a stream of dried nitrogen, the generation reaction unit was thoroughly dried with an open flame. The system was then allowed to cool to room temperature with the dried nitrogen being passed slowly through the system.

The reaction flask was filled with 100 ml of dried tetrahydrofuran* to cover the sintered glass of the dispersion tube. 2,2-Diphenyl-3-cyanothietane 1,1-dioxide (160) (2.3 gm, 0.008 mole) was added and the resulting solution was stirred and cooled in an ice bath.

In the generator were placed 20 ml of diglyme**

* Tetrahydrofuran was freshly distilled over lithium aluminum hydride.

** Diglyme was purified by drying over calcium hydride and then distilled over lithium aluminum hydride.
and 23 ml of purified boron trifluoride etherate* (25.5 gm, 0.18 mole, 50% excess). The addition funnel was filled with a solution of sodium borohydride (3.4 gm, 0.09 mole, 20% excess) in purified diglyme (about 300 ml). Di-borane (0.0375 mole) was generated by slow addition of the sodium borohydride solution to the boron trifluoride etherate and was forced to pass into the solution of 160 by a slight flow of dried nitrogen. After the addition of sodium borohydride solution, the generator was heated for 1 hour at 70-80° to ensure the complete transfer of the diborane to the nitrile solution. The reacting solution was then raised above the ice bath and allowed to return to room temperature. The inlet and the outlet were disconnected, the flask was tightly stoppered and the solution was then stirred at room temperature for two days. The excess diborane was destroyed in an ice bath by careful addition of 10 ml of water. The borane adduct was hydrolyzed by stirring the colorless solution with 20 ml of 10% hydrochloric acid at room temperature for three days. The solution was basified with a cooled solution of 3 gm of sodium hydroxide in 30 ml of water. The mixture was evaporated at room temperature in a rotary evaporator to

* Boron trifluoride diethyl etherate, 100 ml, was purified by adding 2 ml of anhydrous ether and distilling under reduced pressure from 2 gm of granular calcium hydride.
remove most of the tetrahydrofuran. The residual aqueous mixture was extracted with chloroform. The combined chloroform solution was dried and evaporated at room temperature to a viscous liquid (161) (2.40 gm, quantitatively); ir (neat) 705, 760, 1448, 1495, 3020, 3050 (phenyl), 1135, 1310 (sulfone), 1598, 3300 and 3360 (primary amine) cm⁻¹.

The acetamide derivative was prepared by dissolving 0.2 gm (0.007 mole) of the crude 161 in 2.5 ml of acetic anhydride. When the exothermic reaction ceased, the solution was diluted with 15 ml of ice water. The oily deposit was separated by decantation of the aqueous supernatant and solidified by trituration in distilled water with a glass rod. The white precipitate, 2,2-diphenyl-3-acetamidomethylthietane 1,1-dioxide (186) was collected by filtration and washed with distilled water, weighing 0.17 gm (74%). Recrystallization of the product from toluene and subsequently from a mixture of benzene and n-hexane gave needle-like crystals mp 160-170°; ir (KBr) 710, 770, 1450, 1498, 3020, 3065 (phenyl), 1145, 1300 (sulfone), 1675 (amide carbonyl) and 3425 (secondary amide) cm⁻¹; pmr (CDCl₃) δ 1.85 (s, 3, CH₃), 2.72-4.28 (m, 5, SCH₂ and CHCH₂N), 5.70-6.10 (t, broad, 1, NH) and 7.10-7.65 (m, 10, phenyl) ppm.

Attempts to recrystallize the product from a mixture of ethanol and water resulted in desulfonation.

The picrate salt was prepared by dissolving the
crude \textit{161} (0.2 gm, 0.0007 mole) in a minimum amount of 95% methanol (about 1 ml). After filtration, 2 ml of saturated solution of picric acid in 95% ethanol was added. The yellow solution was evaporated to a yellow liquid which was redissolved in 5 ml of absolute methanol. The resulting yellow solution was filtered and the filtrate was cooled in the freezer for a long period until the crystalline picrate salt appeared. The yellow solid (100mg, 24%) was carefully filtered and washed thoroughly with 95% methanol; mp 160.5-164.5°, ir (KBr) 705, 753, 778, 799, 1615 (phenyl), 1142, 1260-1365 (sulfone and nitro) and 2050-3300 (ammonium and carbon-hydrogen stretching) cm\(^{-1}\); pmr (DMSO-\textit{d}_6) \&2.73-4.20 (m, overlapping with solvent impurity peaks, 3, CHCH\_2NH\_), 4.50 (d, broad, 2, SCH\_2, splitting = 7.5 Hz), 7.42 (s, broad, 10, phenyl), 7.97 (m, broad, 3, \textit{NH}_3\_) and 8.65 (s, 2, trinitrophenyl) ppm.

Attempts to recrystallize the picrate resulted in degradation.

5. Synthesis of 2,2-diphenyl-3-dimethylaminomethylthietane 1,1-dioxide (32).

Crude 2,2-diphenyl-3-aminomethylthietane 1,1-dioxide (\textit{161}) (1.9 gm, 0.0063 mole) and 3 ml of 36.4% formaldehyde solution were dissolved in 95% ethanol (100 ml). The resulting solution was stirred at room temperature for 9 hours and then filtered. The filtrate was
transferred into a 400-ml Parr bottle. Seven hundred milligrams of 10% palladium on charcoal was added. The bottle was then placed on a Parr hydrogenation apparatus. The former and the tank were evacuated and filled with hydrogen for 10 times and finally filled with hydrogen to 50 psi. The shaker was started and the methylation was allowed to proceed for 12 hours. After venting the hydrogen from the bottle safely, the ethanol solution was filtered with the aid of "Celite" and the catalyst was washed carefully with ethanol. The filtrate was evaporated at room temperature in a rotary evaporator. The oily residue was mixed with 50 ml of water, basified with a cooled sodium hydroxide solution and extracted with chloroform. The combined chloroform solution was washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated to give a viscous liquid (1.86 gm). This oily material was redissolved in anhydrous ether and the ethereal solution was cooled in a freezing mixture of acetone and dry ice. The solid product which precipitated from ether was collected by filtration. Repeated concentration and cooling of the filtrate gave a total of 0.81 gm (41%) of crude 22, mp 141-152°; ir (KBr) 705, 760, 1445, 1495, 3020, 3050 (phenyl), 1140, 1300 (sulfone) and absence of NH stretching; pmr (CDCl₃) 2.18 (s, 6, N(CH₃)₂), 2.17 (d, 2, CH₂N, J = 8 Hz), 3.20-3.83 (m, 1, CHCH₂S), 3.93-4.35 (m, 2, CH₂S) and 7.05-7.60 (m, 10, phenyl) ppm.
Attempts to further purify the product by column chromatography (neutral alumina/benzene-chloroform-methanol) resulted in unidentified degraded substances.

The picrate salt was prepared by dissolving \( \text{32} \) (0.1 gm) in a minimum amount of absolute methanol. The solution was filtered. A sufficient amount of ethanolic solution of picric acid was added until the formation of turbidity had ceased. Upon standing without disturbance, the solution yielded yellow needle-like crystals. The solvent was carefully withdrawn and the crystalline substance was thoroughly washed several times with 60% aqueous methanol. Finally the bright yellow picrate salt (0.1 gm) was collected by filtration and dried, mp >184.5° (decomp.); ir (KBr) 709, 750, 1460, 1490, 1525, 1544, 1565, 3010, 3040, 3070, 3090 (phenyl and nitro), 1135, 1310, 1360 (sulfone and nitro) and 2050-2850 (ammonium) cm\(^{-1}\); pmr (DMSO-d\(_6\)) \( \delta \) 2.85 (s, 6, N(CH\(_3\))\(_2\)), 3.03-3.35 (m, 2, NCH\(_2\)), 3.50-4.20 (m, 1, CH\(_2\)CH), 4.35-4.87 (m, 2, SCH\(_2\)), 7.38 (m, 10, phenyl), 8.57 (s, 2, trinitrophenyl) and 9.47 (broad, 1, NH) ppm.

Anal. Calcd. for C\(_{24}\)H\(_{24}\)N\(_4\)O\(_9\)S: C, 52.89; H, 4.44; N, 10.37. Found: C, 52.82; H, 4.43; N, 10.18.

The free base \( \text{32} \) was regenerated as white solid by alkalization of the picrate and extraction of the liberated amine by chloroform.

Attempted dimethylation of \( \text{161} \) by using Eschwei-
The lever-Clark procedure (196) was unsuccessful: A solution of crude 161 (0.177 gm, 0.00062 mole), 3.2 gm of 90.7% formic acid (0.06 mole) and 0.1 ml of 37% formaldehyde solution (0.0013 mole) was stirred and heated at 68° for 24 hours. The solution was evaporated to a residue which was basified with sodium carbonate and extracted with chloroform. The chloroform solution was separated and evaporated to remove the solvent. The remaining material was dissolved in 10% hydrochloric acid. After filtration, the acid filtrate was basified (sodium carbonate) and extracted with chloroform. Evaporation of the dried chloroform solution gave a solid, ir (KBr) 710, 760, 925, 1025, 1450, 1490, 2960, 3020 and 3060 cm⁻¹. The ir data obviously indicates the loss of a sulfone group.

6. **Separation of cis-2-butenenitrile (162) and trans-2-butenenitrile (163).**

The commercial 2-butenenitrile (crotononitrile) contained a mixture of cis- (60-70%) and trans- (30-40%) isomers. The two components were separated by repeated distillation through a Spinning-Band-Column distillation apparatus (motor speed 7600 RPM). The purity of the separated isomers (bp: cis, 108°; trans, 121°) were determined by glc (1/8 in x 6 ft stainless steel column packed with 3.2 gm of 15% GE SE-30 on 90 to 100 mesh Anakrom ABS, column temperature 60°).
7. Synthesis of cis-2,2-diphenyl-3-cyano-4-methylthietane (156) and cis-2,2-diphenyl-3-methyl-4-cyanothietane (158).

Freshly recrystallized thiobenzophenone (95) (2.4 gm, 0.0121 mole), pure cis-2-butenenitrile (162) (7.0 gm, 0.105 mole) and redistilled cyclohexane (10 ml) were mixed under a carbon dioxide atmosphere. The solution was tightly sealed and irradiated at 366 nm, a procedure described in the synthesis of 155 (experiment 2). After 152 hours of irradiation the yellow solution obtained was filtered and distilled at room temperature in vacuo to give a viscous liquid (3.6 gm). The distillate containing a mixture of cyclohexane and excess 2-butenenitrile was trapped in a flask cooled in a dry ice-acetone mixture. Analysis by glc showed that the recovered 2-butenenitrile was entirely cis-isomer (162). This revealed that no isomerization of 162 occurred during the photochemical process.

Analysis of the pmr spectrum (CDCl₃) of the viscous liquid obtained above indicated the presence of a 2.5 : 1 mixture of 156 and 158; pmr (CCl₄) 156: δ 1.54 (d, 3, CH₃, J = 7 Hz), 3.80 (m, 1, SCH), 5.00 (d, 1, CHCN, J = 8 Hz) and 7.10-7.75 (m, 10, phenyl) ppm; 158: δ 1.07 (d, 3, CH₃, J = 7 Hz), 4.20 (m, 1, CH₂CH), 4.25 (d, 1, SCH, J = 8 Hz) and 7.10-7.75 (m, 10, phenyl) ppm.

Attempts to separate these two isomers by cry-
stallization and chromatography methods were unsuccessful.

8. **Synthesis of cis-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide (174).**

   The viscous mixture (3.6 gm) of cis-2,2-diphenyl-3-cyano-4-methylthietane (156) and its isomer, cis-2,2-diphenyl-3-methyl-4-cyanothietane (158) prepared by the photocycloaddition of thiobenzophenone (95) (2.4 gm, 0.012 mole) to cis-2-butenenitrile (162) (7.0 gm, 0.105 mole) was dissolved in methylene chloride (50ml). The resulting solution was stirred in a cold water bath and treated with a solution of m-chloroperoxybenzoic acid (85%, 4.58 gm, 0.026 mole) in 150 ml of methylene chloride. After stirring at room temperature for 5 days the oxidation mixture was carefully concentrated under reduced pressure to about 100 ml. The m-chlorobenzoic acid that precipitated was removed by filtration. The filtrate was washed successively with 10% sodium sulfite solution, saturated sodium carbonate solution and water. After drying over anhydrous sodium sulfate, the solution was concentrated again to about 10 ml. Anhydrous ether (10 ml) was added to the residue and the mixture was shaken. The colorless crystalline substance that appeared was collected by filtration and washed with a minimum amount of anhydrous ether. The pmr spectrum of this product showed that it was pure 174.
The yield was 1.75 gm (68.4%).

The material was further purified by recrystallization at room temperature from a mixture of chloroform and n-pentane or from a mixture of methylene chloride and ether to give colorless leaflet crystals, mp 184-186.5°; ir (KBr) 705, 760, 1450, 1496, 1600, 3025, 3060 (phenyl), 1155, 1330 (sulfone), 2260 (nitrile) cm⁻¹; pmr (CDCl₃) δ 1.63 (m, 3, CH₃), 4.40-4.80 (m, 2, CHCN and SCH) and 7.20-7.60 (m, 10, phenyl) ppm.

Anal. Calcd. for C₁₇H₁₅NSO₂: C, 68.66; H, 5.08; N, 4.71.  
Found: C, 68.69; H, 5.09; N, 4.76.

The ethereal mother liquid from which 174 was isolated, was evaporated to an oil. The pmr spectrum of this oily substance indicated that no appreciable amount of cis-2,2-diphenyl-3-methyl-4-cyanothietane 1,1-dioxide (175) existed.


A crude liquid (7.3 gm) of cis-2,2-diphenyl-3-cyano-4-methylthietane (156) prepared by the photocycloaddition reaction in experiment 7 was dissolved in a minimum amount of anhydrous ether and a solution of m-chloroperoxybenzoic acid (9.7 gm) in 20 ml of anhydrous ether was added with stirring. After the addition of peracid precipitation occurred. The resulting mixture was placed aside
overnight and filtered to give a white powder \((178)\) (3.03 gm), mp 135-136°; ir (KBr) 708, 762, 1450, 1500, 1600, 3040, 3070 (phenyl), 1080 (S=O \((172)\)), and 2260 (cyano) cm\(^{-1}\); pmr (CDCl\(_3\)) \(6\) 1.67 (d, 3, CH\(_3\), \(J = 7\) Hz), 3.41 (two overlapping doublets centered at 199.5 and 210.1 Hz respectively, 1, SCH, \(J(CH-CH) = 10\) Hz, \(J(CH_3-CH) = 7\) Hz), 4.71 (d, 1, CNCH, \(J = 10\) Hz) and 7.40 (m, 10, phenyl) ppm.

Oxidation of the sulfoxide \(178\) in chloroform with excess m-chloroperoxybenzoic acid gave corresponding sulfone \(174\).

10. Synthesis of cis-2,2-diphenyl-3-aminomethyl-4-methylthietane \(1,1\)-dioxide \((179)\).

The procedure described in the experiment 4 was used. A stream of diborane (0.0375 mole) generated by addition of sodium borohydride (3.4 gm, 0.09 mole) to boron trifluoride etherate (25.5 gm, 0.18 mole) was slowly passed into a stirred and cooled solution of \(174\) (3.3 gm, 0.01 mole) in 200 ml of dried tetrahydrofuran. The colorless solution was stirred at room temperature for 48 hours. The excess diborane was destroyed with 10 ml of water, 27 ml of 20% aqueous hydrochloric acid was added and the resulting solution was stirred for 40 hours. After alkalization to pH 12 with sodium hydroxide solution, the aqueous mixture was evaporated at room temperature to remove the tetrahydrofuran. The remaining aqueous mixture was extract-
ed with chloroform. The chloroform extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The crude 179 (2.84 gm, 86%) was obtained as a gummy substance after evaporation of the solvent and drying in vacuo. A sample of this gummy material was grossly purified by dissolving in a mixture of methanol and n-pentane and allowing the solution to be concentrated spontaneously at room temperature to give colorless needle-like crystals (179), mp 136-143°; ir (KBr) 710, 763, 780, 1450, 1495, 3030, 3060 ( phenyl), 1140, 1155, 1300, 1320 (sulfone), 3325 and 3385 (primary amine) cm⁻¹; pmr (CDCl₃) δ 0.98 (s, broad, 2, NH₂, exchanged by D₂O), 1.53 (d, 3, CH₃, J = 7 Hz), 2.89 (d, broad, 2, CH₂N, J = 7 Hz), 3.50 (m, 1, NCH₂CH, J(CH₂-CH) = 7 Hz, J(CH-CH) = 9 Hz), 4.53 (m, 1, SCH, J(CH₃-CH) = 7 Hz, J(CH-CH) = 9 Hz) and 7.42 (m, 10, phenyl) ppm.

The picrate salt was prepared by dissolving the crude 179 in a minimum amount of 95% ethanol. Addition of an ethanolic solution of picric acid gave the yellow crystalline picrate which was recrystallized several times from a mixture of 95% ethanol and 10% acetic acid, mp 198-201°; ir (KBr) 715, 755 ( phenyl), 1495, 1530, 1555, 1610, 1630 (phenyl and nitro), 1210-1400 (sulfone and nitro) and 2150-3420 ( ammonium) cm⁻¹; pmr (DMSO-d₆) δ 1.51 (d, 3, CH₃, J = 7 Hz), 2.95 (d, broad, 2, CH₂N, J = 7 Hz), 3.82-4.35 (m, 1, NCH₂CH), 4.40-5.15 (m, 1, SCH), 7.43 (s, 10, phenyl
7.87 (s, broad, 3, NH$_3$) and 8.72 (s, 2, trinitrophenyl) ppm.

**Anal. Calcd. for C$_{23}$H$_{22}$N$_4$SO$_2$: C, 52.07; H, 4.18; N, 10.56.**
**Found: C, 52.29; H, 4.21; N, 10.69.**

11. **Synthesis of cis-2,2-diphenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide (33).**

A mixture of crude 2,2-diphenyl-3-aminomethyl-4-methylthietane 1,1-dioxide (179) (2.5 gm, 0.0083 mole), formaldehyde solution (3 ml of 36.4%) and 95% ethanol (100 ml) was stirred at room temperature for 9 hours and then filtered. To the filtrate were added 0.49 ml of glacial acetic acid and 0.7 gm of 10% palladium on charcoal. The resulting mixture was immediately shaken at 50 psi of hydrogen, a procedure described in experiment 5. After 11 hours of methylation the dark mixture was filtered with the aid of "Celite". The solvent and the excess formaldehyde were removed at room temperature by vacuum evaporation. The residue was basified with sodium hydroxide solution and extracted with ether. The pooled ether extract was washed with saturated sodium chloride solution, filtered and dried. Crude 33 was obtained as a viscous liquid (3.0 gm) after evaporation of the ether in a rotary evaporator. The ir spectrum of this crude product showed the absence of N-H stretching of the primary amino group. White hydrochloride precipitate (mp 120-150°) was
obtained when a sample of the crude tertiary amine dissolv-
ed in ether was treated with an ethereal solution of hydro-
gen chloride. This hydrochloride salt deteriorated rapidly
in chloroform. A sample of 0.02 gm of the hydrochloride was
very soluble in about 0.4 ml of CDCl$_3$ but an insoluble ma-
terial rapidly crystallized out from the chloroform solu-
tion in one or two minutes. This crystalline material, dif-
ferent from the original material, was insoluble in most
common laboratory solvents. The ir spectrum showed that
this material was a hydrochloride and sulfone but was dif-
ferent from the original hydrochloride.

The crude 33 (0.50 gm) was purified by using co-
llumn chromatography (neutral alumina/benzene). The isolat-
ed pure product was solidified upon addition of n-pentane.
A white solid (33) was obtained, mp 132-135°; ir(KBr) 702,
715, 752, 1445, 1456, 1495, 1596, 3020, 3050 (phenyl), 1135
and 1300 (sulfone) cm$^{-1}$; pmr(CDCl$_3$) 6 1.53 (d, 3, CH$_3$, J =
7 Hz), 2.20 (s, 6, N(CH$_3$)$_2$), 1.83-2.77 (m, 2, NCH$_2$), 3.18-
3.92 (m, 1, NCH$_2$CH), 4.20-4.83 (two overlapping quartets
centered at 265.0 and 274.5 Hz respectively, 1, SCH, J(CH-
CH) = 9 Hz) and 7.38 (m, 10, phenyl protons) ppm.

The picrate salt was prepared by dissolving 33 in
a minimum amount of methanol. Addition of ethanolic solu-
tion of picric acid yielded a yellow precipitate which was
collected and recrystallized from a mixture of methanol and
acetone to give fine, needle-like crystals, mp 212-214°; ir
(KBr) 705, 752 (phenyl), 1150, 1210-1385 (sulfone and nitro), 1490, 1560, 1615 (nitro and phenyl), and 2100-3100 (ammonium) cm⁻¹; pmr (DMSO-d₆) δ1.52 (d, 3, CH₃, J = 7 Hz), 2.90 (s, broad, 6, N(CH₃)₂), 3.00-3.30 (broad band, 2, NCH₂), 3.80-4.40 (m, 1, NCH₂CH), 4.50-5.10 (m, 1, SCH), 7.45 (m, 10, phenyl protons), 8.63 (s, 2, trinitrophenyl protons), and 9.37 (broad band, NH) ppm.

Anal. Calcd. for C₂₅H₂₆N₄SO₉: C, 53.76; H, 4.69; N, 10.03. Found: C, 53.79; H, 4.82; N, 10.23.

12. Synthesis of trans-2,2-diphenyl-3-cyano-4-methylthietane (157) and trans-2,2-diphenyl-3-methyl-4-cyanothietane (159).

Freshly recrystallized thiobenzophenone (95) (1.1 gm, 0.0056 mole), glc-pure trans-2-butenenitrile (163) (3.16 gm, 0.0471 mole), and redistilled cyclohexane (4.5 ml) were mixed under a carbon dioxide atmosphere. The solution was tightly stoppered and irradiated at 366 nm, a procedure described in the synthesis of 2,2-diphenyl-3-cyanothietane (155). The resulting yellow solution was filtered and evaporated in vacuo to give a viscous liquid (1.7 gm). The solvent and the excess 2-butenenitrile were recovered in a cold trap. Analysis by glc indicated that no isomerization of 163 occurred in the photochemical process and only 163 was recovered.

Analysis of the pmr spectrum of the viscous li-
quid indicated the existence of an isomeric mixture of trans-2,2-diphenyl-3-cyano-4-methylthietane (157) and trans-2,2-diphenyl-3-methyl-4-cyanothietane (159) in a ratio of 2.8:1; pmr (CCl₄) 157: δ 1.45 (d, 3, CH₃, J = 6 Hz), 3.86 (m, 1, CH₂CH), 4.36 (d, 1, CNCH, J = 10 Hz), and 6.80-7.80 (m, 10, phenyl protons) ppm; 159: δ 0.83 (d, 3, CH₃, J = 6 Hz), 3.66 (d, 1, CNCH, J = 10 Hz), 3.86 (m, 1, CH₂CH) and 6.80-7.80 (m, 10, phenyl protons) ppm.

Attempts to separate the two isomers by chromatography or by crystallization were unsuccessful.


The crude mixture (1.7 gm) of trans-2,2-diphenyl-3-cyano-4-methylthietane (157) and trans-2,2-diphenyl-3-methyl-4-cyanothietane (159) prepared by the photocycloaddition of thiobenzophenone (95) (1.1 gm, 0.0056 mole) to trans-2-butenenitrile (163) (3.16 gm, 0.0471 mole) was dissolved in methylene chloride (50 ml). The solution was stirred in a cold water bath and treated with a solution of m-chloroperoxybenzoic acid (2.13 gm, 0.0123 mole) in methylene chloride (150 ml). The reaction mixture was stirred for 5 days. The excess m-chloroperoxybenzoic acid and its product m-chlorobenzoic acid were removed by washing successively with 10% sodium sulfite, saturated sodium carbonate, and saturated sodium chloride solutions. The organic
solution was then dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue obtained was chromatographed on silica gel (benzene) to give trans-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide (176) as a white solid (0.88 gm, 52.8%). No appreciable amount of other isomer, trans-2,2-diphenyl-3-methyl-4-cyanothietane 1,1-dioxide (177) was detected.

The isolated product was recrystallized three times from a mixture of chloroform and n-pentane to give a colorless crystalline substance (176), mp 167.2-171°; ir (KBr) 710, 735, 755, 774, 1450, 1498, 1600, 3030, 3060 (phenyl), 1148, 1318 (sulfone), and 2260 (nitrile) cm⁻¹; pmr (CDCl₃) δ 1.63 (d, 3, CH₃, J = 6.6 Hz), 3.78 (d, 1, CNCH, J = 10 Hz), 4.92 (two overlapping quartets centered at 290.0 and 300.8 Hz respectively, 1, SCH, J(CHCH) = 10 Hz, J(CH₂CH) = 7 Hz) and 7.42 (m, 10, phenyl protons) ppm. Anal. Calcd. for C₁₇H₁₅NSO₂: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.57; H, 5.20; N, 4.84.


A stream of diborane (0.0375 mole) generated by addition of sodium borohydride (3.4 gm, 0.09 mole) to boron trifluoride etherate (25.5 gm, 0.18 mole) was slowly passed into a stirred and ice-cooled solution of trans-2,2-diphenyl-3-cyano-4-methylthietane 1,1-dioxide (176) (1.37 gm,
0.0046 mole) in 100 ml of dried tetrahydrofuran. The reacting mixture was stirred at room temperature for 2 days, 10 ml of water was added to inactivate the excess diborane, 20 ml of 10% hydrochloric acid followed and the resulting mixture was stirred for 3 days to hydrolyze the borane adduct. Then a cold solution of 3 gm of sodium hydroxide in 30 ml of water was added. The resulting basic mixture was evaporated at room temperature to remove most of the tetrahydrofuran. The product was extracted from the remaining aqueous mixture with chloroform. The chloroform solution was washed with saturated sodium chloride solution and dried. Removal of the solvent from the chloroform extract gave trans-2,2-diphenyl-3-aminomethyl-4-methylthietane 1,1-dioxide (180) as a gummy substance (1.69 gm); ir (neat) 710, 738, 760, 1450, 1500, 3030, 3060 (phenyl), 1145, 1303 (sulfone), 3320 and 3380 (primary amine) cm⁻¹.

The picrate salt was prepared by addition of an ethanolic solution of picric acid to a methanolic solution of 180 (0.1 gm). Upon standing the resulting solution for one hour without disturbance, the yellow crystalline picrate that appeared was collected by filtration and washed thoroughly with 50% aqueous methanol. After drying, the picrate salt (0.1 gm) was pure enough for elemental analysis, mp 168.5-170.5°; ir (KBr) 710, 733, 752 (phenyl), 1150, 1200-1400 (nitro and sulfone), 1400-1650 (nitro and phenyl) and 2100-3300 (ammonium and C-H) cm⁻¹; pmr (DMSO-d₆) δ1.50 (d, 3, CH₃, J = 7 Hz), 2.70-4.0 (m, NCH₂, CH₂CH and
solvent impurities), 4.85 (qd, 1, SCH, $J_{(CH_2CH)} = 7$ Hz, $J_{(CHCH)} = 9$ Hz), 7.0-7.7 (m, 10, phenyl protons), 8.60 (s, 2, trinitrophenyl protons) ppm.

Anal. Calcd. for $C_{23}H_{22}N_4SO_9$: C, 52.07; H, 4.18; N, 10.56. Found: C, 52.18; H, 4.42; N, 10.61.

Recrystallization of the picrate from a mixture of acetone and methanol resulted in a depressed melting point and the appearance of carbonyl absorption in the ir spectrum.

The N-acetyl derivative was prepared by reacting 180 (0.15 gm) with acetic anhydride (0.5 ml) for 15 minutes. The gummy substance that appeared upon diluting the anhydride solution with 10 ml of cooled water, was separated by decantation of the aqueous solution and then purified by using a silica gel column (30 gm, eluted successively with chloroform and methanol). The acetamide which was isolated as a colorless solid was then recrystallized several times from benzene to give the colorless crystalline trans-2,2-diphenyl-3-acetamidomethyl-4-methylthietane 1,1-dioxide, mp 182-185°; ir (KBr) 710, 738, 758, 1448, 1500, 1540, 3060 (phenyl), 1145, 1300 (sulfone), 1650 (amide carbonyl) and 3330 (secondary amide) cm$^{-1}$; pmr (CDCl$_3$) $\delta$ 1.52 (d, 3, CHCH$_3$, $J = 7$ Hz), 1.83 (s, 3, COCH$_3$), 2.93-3.37 (m, 3, CHCH$_2$N), 4.10-4.60 (m, 1, SCH), 5.40 (t, broad, NH), and 7.38 (s, 10, phenyl protons) ppm.
15. Synthesis of trans-2,2-diphenyl-3-dimethylaminomethyl-4-methylthietane 1,1-dioxide (34).

The crude trans-2,2-diphenyl-3-aminomethyl-4-methylthietane 1,1-dioxide (180) (1.49 gm, 0.00428 mole) prepared in the previous experiment was dissolved in 2.5 ml of 36.4% formaldehyde solution and 80 ml of 95% ethanol. The resulting solution was stirred for 10 hours and then filtered. To the filtrate were added 0.4 ml of glacial acetic acid and 0.5 gm of 10% palladium on charcoal. The resulting mixture was shaken in a Parr hydrogenation bottle at 50 psi of hydrogen for 11 hours, and then carefully filtered. The filtrate was basified, the solvent was evaporated and the residue was extracted with chloroform. The chloroform solution was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated at room temperature to an oil to which was added a small amount of anhydrous ether to precipitate the crude product. After filtration, 34 was obtained as a white solid (0.92 gm, 65%) which was rapidly chromatographed on neutral alumina (chloroform) to give a gummy substance which was solidified by trituration in a small amount of methanol and recrystallized at room temperature as follows: The material (34) was dissolved in methylene chloride, the solution was carefully concentrated to a very small volume in a rotary evaporator, a small amount of methanol was added, and the solution was set aside for several hours. A crystalline
substance which appeared during this period was collected and treated by repeating the above procedure. Consequently 34 was obtained as colorless crystals, mp 125.5-130.5°; ir (KBr) 702, 712, 760, 1447, 1500, 1600, 3030, 3050, 3065 (phenyl), 1143, 1153 and 1293 (sulfone) cm⁻¹; pmr (CDCl₃) δ 1.58 (d, 3, CH₃, J = 7 Hz), 2.06 (obscured doublet, 2, NCH₂), 2.14 (s, 6, N(CH₃)₂), 2.74-3.33 (m, 1, NCH₂CH), 4.38 (two overlapping quartets centered at 257.50 and 268.25 Hz respectively, 1, SCH, J(CHCH) = 10 Hz, J(CHCH₃) = 7 Hz) and 7.37 (m, 10, phenyl protons) ppm.

Anal. Calcd. for C₁₉H₂₃NSO₂: C, 69.27; H, 7.04; N, 4.25. Found: C, 68.97; H, 6.77; N, 4.10.

The picrate salt was prepared by reacting a solution of 34 (0.1 gm) in a minimum amount of methanol with picric acid (0.3 ml of saturated ethanolic solution). The crystalline picrate was collected and washed with methanol, mp 184-188°.


To a stirred solution of 2,2-diphenyl-3-cyanothietane (155) (2.0 gm, 0.008 mole) in 60 ml of dried tetrahydrofuran was added 0.025 mole of borane-methyl-sulfide complex (2 ml, neat liquid, containing about 5% methyl sulfide). The reacting mixture was stirred for 24 hours and then hydrolyzed for 20 hours by stirring the solution...
in a mixture of 10 ml each of water and concentrated hydrochloric acid. After evaporating most of the tetrahydrofuran, the remaining aqueous mixture was extracted with chloroform. The hydrochloride in the chloroform solution was converted into free amine by shaking the solution with sodium carbonate solution. The chloroform solution was then washed with saturated sodium chloride solution, dried, and evaporated to a pale yellow liquid (2.3 gm), ir (neat) 710, 760, 775, 1450, 1493, 3025, 3060 (phenyl), 1600, 3300 and 3360 (primary amine) cm⁻¹.

The crude amine was dissolved in anhydrous ether. The solution was filtered. To the filtrate was added a sufficient amount of ethereal solution of hydrogen chloride to precipitate the crude hydrochloride salt, which was then collected and dried, weighing 0.9 gm, mp >149° (decomp.); ir (KBr) 710, 755, 780, 1448, 1495 (phenyl), 1600 and 2100-3300 (ammonium) cm⁻¹; pmr (CDCl₃) δ 7.15 (phenyl protons) and 8.15 (NH₃, exchanged by D₂O) ppm.

Attempted catalytic methylation of the hydrochloride by using formaldehyde, 10% palladium on charcoal and 50 psi of hydrogen was unsuccessful.

The crude hydrochloride was methylated by repeated formylation and reduction method (151). The hydrochloride (0.8 gm) was dissolved in 2 ml of formic acid and a minimum amount of ether. The solution was cooled in an ice bath, a cooled solution of formic-acetic anhydride prepared
from dried formic acid (5.1 ml) and acetic anhydride (10 gm) (197) was added and the resulting mixture stirred at room temperature overnight. After evaporating the ether, the anhydride solution was added dropwise into an ice-water mixture. A gummy deposit which appeared was extracted with chloroform. The chloroform solution was washed with water, dried and then evaporated to a viscous liquid (0.65 gm); ir (neat) 710, 765, 1450, 1498, 3010, 3060 (phenyl), 1675 (amide carbonyl), 1600 and 3300 (secondary amide) cm$^{-1}$. The ir data indicated that the product was a secondary amide. An ice-cooled solution of this amide (0.65 gm) in tetrahydrofuran was reduced by addition of lithium aluminum hydride (0.4 gm). The mixture was stirred at ice temperature for 6 hours. The solvent was evaporated, the lithium aluminum hydride was inactivated by sodium sulfate solution and the resulting mixture was then extracted with chloroform. Subsequent washing, drying, and evaporation of the chloroform solution resulted in a pale yellow liquid (0.5 gm); ir (neat) 710, 760, 1450, 1495, 3025, 3060 (phenyl), 1600, and 3310 (secondary amine) cm$^{-1}$. The ir data indicated that the secondary amide was reduced to a secondary N-methyl amine. This secondary amine was formylated by using the same method to give a tertiary formamide (0.4 gm); ir (neat) 710, 760, 1450, 1495, 3020, 3060 (phenyl) and 1670 (amide carbonyl) cm$^{-1}$. Subsequent reduction of the tertiary amide with lithium aluminum hydride
by employing the above method gave a crude N,N-dimethyl-
amine as a pale yellow liquid (0.3 gm); ir (neat) 710,
760, 1450, 1498, 1600, 3030, 3060 and 3090 (phenyl) cm⁻¹. The absence of the carbonyl absorption indicated that the formamide was reduced. The crude tertiary amine was grossly purified by column chromatography (neutral alumina/ chloroform). The isolated liquid substance (0.2 gm) was dissolved in dried ether and treated with a dried ethereal solution of hydrogen chloride. The hydrochloride precipitate formed was collected, weighing 0.1 gm after drying in vacuo; mp > 70°; ir (KBr) 740, 760, 1498, 1505, 1600, 3040, 3060 (phenyl), and 2200-2800 (NH) cm⁻¹; pmr (CDCl₃) δ 2.73 (s, 6, N(CH₃)₂), 2.35-3.40 (m, 4, NCH₂ and SCH₂), 4.10 (m, 1, SCH₂CH), 5.88 (s, broad, 1, NH, exchanged with D₂O) and 7.33 (s, broad, 10, phenyl) ppm. The spectroscopic data indicated that the isolated hydrochloride salt was a crude material of 2,2-diphenyl-3-dimethylaminomethylthietane hydrochloride (191). Attempts to further purify this material by crystallization were unsuccessful.

17. Synthesis of N,N-dimethylallylamine (200).

A stirred mixture of allylamine (25.2 gm, 0.30 mole), 90% formic acid (66.8 gm, 1.26 mole) and 37% formaldehyde solution (86 ml, 1.2 mole) was heated at 90° for 24 hours. Thirty milliliters of concentrated hydrochloric acid was added. The mixture was concentrated under reduced
pressure to 150 ml, then basified with sodium carbonate, and extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate, bubbled with hydrogen chloride to convert the free amine into its salt and finally stripped off the chloroform by evaporation. The residual liquid (31.2 gm) was cooled (-9°) and basified with a cool solution of 12 gm of sodium hydroxide in 12 ml of water. The tertiary amine (16.6 gm) was then grossly distilled in vacuo and trapped in a flask cooled in a dry ice-acetone mixture. After repeated redistillation at atmospheric pressure, N,N-dimethylallylamine (200) was obtained as a colorless liquid (13.5 gm, 40%), bp 65-66° (lit. (198) 64° (743 mm)); pmr (neat) δ 2.20 (s, 6, N(CH3)2), 2.80-3.08 (m, 2, NCH2), 4.95-5.40 (m, 2, =CH2) and 5.56-6.30 (m, 1, =CH) ppm. The uv spectrum of this amine did not show absorption at 366 nm, the wavelength employed to prepare the thietane derivatives by photocycloaddition of thiobenzophenone to olefins.

18. Attempted photocycloaddition of thiobenzophenone (95) to N,N-dimethylallylamine (200).

A mixture of N,N-dimethylallylamine (200) (8.6 gm, 0.077 mole), freshly recrystallized thiobenzophenone (95) (4.80 gm, 0.024 mole) and 250 ml of anhydrous ether was irradiated at 366 nm for 211 hours, a procedure being described in the synthesis of 2,2-diphenyl-3-cyanothietane.
A sample of the decolorized solution (50 ml) was evaporated to an oil (1.48 gm). Analysis by thin layer chromatography (neutral alumina, chloroform) indicated the presence of at least seven components. Attempts to prepare a picrate derivative or to separate the different components by using column chromatography method were unsuccessful. A white solid was obtained when HCl-ether was added to an ethereal solution of the above crude oil, mp >91° (decomp.). The pmr spectrum showed that the material was not the expected product. Oxidation of the crude photoaddition products with m-chloroperoxybenzoic acid gave a crude mixture exhibiting carbonyl and sulfonyl absorption in the ir spectrum.


The method used was taken from a patent (152). Thirty-one milliliters (47 gm) of chlorine was collected in a graduated cylinder cooled at -80°. The yellow chlorine liquid was slowly boiled at about -30°, and the chlorine vapor was passed into a stirred and ice-cooled solution of β-mercaptoethanol (16.6 gm, 0.213 mole) in 1,2-dichloroethane (30 gm). After 13 ml of chlorine had been passed into the thiol solution, 4 ml of water was added dropwise to the reacting mixture simultaneously. When the transfer of the remaining chlorine was completed, the excessive halogen in the reacting mixture was expelled with
a stream of nitrogen. A small amount of liquid (ca. 2 ml) that separated from the mother liquid was removed. The mother solution was dried over anhydrous sodium sulfate, filtered and evaporated. The resulting residue was distilled to give 29.2 gm (84%) of β-chloroethanesulfonyl chloride (212), bp 52-54° (0.2 mm) (lit. (152) 80° (1-2 mm); 94%). Redistillation of the product (29 gm) gave a colorless liquid (212) (21 gm) bp 40.5° (0.01 mm), ir (neat) 670, 710 (chloro), 1165 and 1370 (sulfonyl) cm⁻¹; pmr (neat) δ 3.75-4.40 (m, CH₂CH₂S) ppm.

20. Reaction of β-chloroethanesulfonyl chloride (212) and β-dimethylaminostyrene (213).

A mixture of β-dimethylaminostyrene (213) (2.21 gm, 0.015 mole), purified triethylamine (3.02 gm, 0.03 mole) and 20 ml of dried ether was stirred and cooled in a dry ice-acetone bath at -80°, a solution of 2.45 gm (0.015 mole) of β-chloroethanesulfonyl chloride (212) in 20 ml of dried ether was added dropwise and the reaction was allowed to proceed for 1 ½ hours during which a white precipitate appeared. The resulting mixture was allowed to return to room temperature and filtered to give a white solid material which was identified as triethylamine hydrochloride. The filtrate was evaporated to a brownish yellow mass, 10 ml of dried ether was added and the ethereal solution was chilled yielding 1.1 gm of solid. The
pmr spectrum showed that it contained mainly \( \delta \)-(vinylsulfonyl)-\( \beta \)-dimethylaminostyrene (218) and a little amount of triethylamine hydrochloride. The filtrate was evaporated to a brownish yellow semi-solid (1.44 gm). Infrared analysis indicated that this material contained mainly 218. The calculated yield of the total triethylamine hydrochloride obtained was quantitative (0.03 mole). This indicated that one mole of \( \beta \)-chloroethanesulfonyle chloride was dechlorinated by two moles of triethylamine and the expected cyclic product was not produced.

The crude 218 was dissolved in ether, the ethereal solution was washed successively with sodium carbonate solution and water. The solvent was evaporated and the residue was recrystallized four times from anhydrous ether to give the pure 218 as colorless leaflet crystals, mp 102-105°; ir (KBr) 722, 740, 1443, 1500 (phenyl), 1185, 1258 (vinyl CN), 855, 958, 970, 990, 1620, 3035, 3065 (double bond), 1120, 1135 and 1300 (sulfone) cm\(^{-1}\); pmr (CDCl\(_3\)) \( \delta \) 2.68 (s, 6, N(CH\(_3\))\(_2\)), 5.50-6.80 (m, 3, CHCH\(_2\)), 7.33 (s, 5, phenyl) and 7.37 (s, 1, NCH) ppm.

Anal. Calcd. for C\(_{12}\)H\(_{15}\)NO\(_2\)S: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.73; H, 6.29; N, 5.86.

The sodium fusion test for the presence of chlorine was negative.

Repeating the experiment by using an equimolar amount of triethylamine at temperature of -80, 0, or 25°
also resulted in the isolation of 218. No appreciable amount of cyclization product was observed. Addition of a mixture of triethylamine and 213 to the solution of 212, a reversed addition procedure, also gave same results.


Methyl propargyl ether was synthesized according to a method taken from literature (157). A mixture of redistilled propargyl alcohol (89 gm, 1.59 mole), 71 ml of water and 176 gm of 50% (w/v) aqueous sodium hydroxide solution was heated at 40°. The solution was stirred and 120 gm of dimethyl sulfate (120 gm, 0.95 mole) was added in slowly so that the temperature of the solution was maintained below 60°. The mixture was heated at 50-60° for 2 hours, and then distilled at atmospheric pressure to give 57.9 gm (61%) of methyl propargyl ether (217), bp 60-61.5°; pmr (neat) δ 2.62 (t, 1, CH, J = 2.5 Hz), 3.33 (s, 3, CH₃), and 4.14 (d, 2, CH₂, J = 2.5 Hz) ppm.

22. Synthesis of methoxyallene (113).

Methoxyallene (113) was prepared according to the method described by Hoff et al. (156). A mixture of methyl propargyl ether (217) (52 gm, 0.866 mole) and potassium t-butoxide (7.15 gm, prepared by refluxing t-butyl alcohol and potassium and evaporating the excessive alcohol in vacuo) was heated at 70° for two hours. The mixture was
distilled at atmospheric pressure to give 32.5 gm (63%) of methoxyallene (113), bp 50.8-51.5°; pmr (neat) δ 2.93 (s, 3, CH₃), 5.00 (d, 2, CH₂, J = 5.5 Hz), and 6.30 (t, 1, CH, J = 5.5 Hz) ppm.

23. Synthesis of 2,2-diphenyl-3-methoxy-4-methylenethietane (114).

A very brief note taken from literature (134a) was used as a reference. Freshly recrystallized thiobenzophenone (95) (5 gm, 0.025 mole) and purified methoxyallene (113) (7.2 gm, 0.1 mole) were dissolved in 280 ml of anhydrous ether reagent. The blue color of thiobenzophenone completely disappeared within 3½ hours at room temperature. The solvent was removed by evaporation. To the oily residue was added about 100 ml of ether-n-pentane solution (2:3) and the resulting precipitates was filtered to give 2-methoxymethylene-6-phenyl-benzo(d)thiane (115) as a pale yellow solid (>3.5 gm, >50%) (lit. (134a) 15-20%): pmr (CDCl₃) δ 3.42 (s, 2, CH₂), 3.60 (s, 3, OCH₃), 5.31 (s, 1, CHS), 6.15 (s, 1, CHO) and 7.1-7.6 (m, 9, phenyl protons) ppm. The pmr data was identical to that reported in the literature.

The filtrate was evaporated to a semi-solid. Analysis by using thin layer chromatography method (neutral alumina; CCl₄) indicated the presence of two major components and some impurities. One major component was benzo-
thiane 115, another was 2,2-diphenyl-3-methoxy-4-methylene-thietane (114). The pmr spectrum (CDCl₃) of this mixture showed that in addition to the signals accounted for by 115 and other impurities, signals at 6 3.33 (s), 4.98 (t, splitting = 2.5) and 5.38 (m) ppm were comparable to the literature pmr data of 114 (lit. (134) (CCl₄) 3.21 (s), 4.91 (t, J = 2.3 Hz), 5.24 (t, J = 2.3 Hz), and 5.35 (t, J = 2.2 Hz) ppm).

An experiment was carried out to prove that the reaction of 113 and 95 was a thermal reaction: A 50-ml solution of 95 (0.1 M) in dried and thiophene-free benzene was tightly sealed with a rubber septum, wrapped in aluminum foil and placed in a dark place to protect the solution from light. Methoxyallene (113) (1.44 gm, 0.02 mole) measured in a syringe was injected into the solution which was then shaked thoroughly. The blue color disappeared within 1½ hours and the solution became yellow. Tlc analysis indicated that the products were the same as obtained above.

In another experiment, two pyrex flasks each containing 100-ml of a solution of 95 (0.1 M) in thiophene-free benzene were sealed with rubber septa and placed in a dark hood. After addition of 113 (2.88 gm, 0.01 mole), the solutions were immediately irradiated with uv light generated from a medium pressure mercury arc (450 W) filtered through a 3% potassium dichromate solution. The blue color of the reacting mixture remained very intense after 20 mi-
nutes of irradiation, but completely disappeared by 1\frac{1}{2}
hours. This was incompatible with the report that the re-
action was complete during 20 minutes of irradiation (134a).
Analysis by using thin layer chromatography indicated the
presence of the same products and work up gave comparable
yields of benzothiane 115 and thietane 114.

The isolated benzothiane 115 was not stable at
room temperature. Tlc analysis indicated that 115 was com-
pletely decomposed upon evaporating a solution of 115
(about 10 mg) in chloroform (1 ml) during a period of 24
hours. Attempts to purify 115 by using column chromatogra-
phy (neutral alumina or silica gel) resulted in the isola-
tion of several unidentified materials. No appreciable
amount of 115 could be recovered.

Attempts to isolate 2,2-diphenyl-3-methoxy-4-me-
thylenethietane (114) by using liquid column chromatogra-
phy was also unsuccessful. Repeated chromatography of 1 gm
of mixture containing 114 by employing Dry Column Chroma-
tography method (158) (neutral alumina containing 4-5% wa-
ter; benzene or CCl$_4$ used as solvent) resulted in isolation
of only a small amount of crude 114 (about 20 mg). The in-
stability of both 114 and 115 caused the difficulty in the
isolation of the former.

24. Attempted hydroxylation of 2,4-diphenylthiete 1,1-
dioxide (227) with sodium hydroxide. Isolation of
To a stirred mixture of 2,4-diphenylthiete 1,1-dioxide \((227) (0.5 \text{ gm}, 0.002 \text{ mole}) (84)\), 3 ml of water and 10 ml of dimethylsulfoxide, was added a solution of 1 gm of sodium hydroxide in 20 ml of 50% aqueous dimethylsulfoxide solution. The resulting greenish solution was stirred at room temperature for 5 hours and then cooled in the refrigerator for 3 days in an attempt to induce crystallization of the desired 2,4-diphenyl-3-hydroxythietane 1,1-dioxide \((235)\). When solid failed to separate, the solution was then diluted with 75 ml of water and extracted with ether \((150 \text{ ml})\). The ethereal solution was separated, dried over anhydrous sodium sulfate and finally evaporated to give a yellow solid \((0.4 \text{ gm})\). Recrystallization from a mixture of ether and n-pentane gave colorless needle-like crystals, mp 148-152°; ir \((\text{KBr})\) 706, 716, 738, 770, 1458, 1498, 1604, 3028, 3058 (phenyl), 1135 and 1308 (sulfone) \(\text{cm}^{-1}\); pmr \((\text{CDC}_3)\) δ 4.10 \((s, 4, \text{CH}_2)\) and 7.4 \((s, 10, \text{phenyl})\) ppm. The ir and mp data were in accord with the literature data \((198, 199)\) of dibenzylsulfone \((234)\). The yield was 81%.

Repeating the experiment at room temperature for 16 hours without refrigeration resulted in the isolation of the same product.

25. Reaction of 2,4-diphenylthiete 1,1-di-
oxide (227) with sulfuric acid. Isolation of 3,5-
diphenyl-1,2-oxathiacyclopenta-3-ene 2-oxide (243, 244).

2,4-Diphenylthiete 1,1-dioxide (227) (1.0 gm, 0.0039 mole) was dissolved in 15 ml of stirred and cooled
(-5°) concentrated sulfuric acid. The resulting brown so-
lution was added dropwise into 150 ml of water while stir-
red and cooled in an ice bath. The white precipitate that
appeared upon dilution of the acid was separated by decan-
tation. The decanted supernatant was extracted with ether
and the ethereal extract was returned to the precipitate.
More ether was added to dissolve the precipitate complete-
ly. The ethereal solution was then dried over anhydrous
sodium sulfate and evaporated under reduced pressure to
give a solid material (1 gm, 100%). The ir, pmr and tlc
data indicated that this material was a mixture of two
isomeric sulfinites, 3,c-5-diphenyl-1,r-2-oxathiacyclopenta-
ta-3-ene 2-oxide (243) (59.6%) and 3,t-5-diphenyl-1,r-2-
oxathiacyclopenta-3-ene 2-oxide (244) (40.4%). The percen-
tage was determined on the basis of the signals attributed
to the benzylic protons in the pmr spectra. These two com-
ponents were separated by using column chromatography (si-
lica gel, chloroform) and recrystallized from anhydrous
ether: 3,c-5-diphenyl-1,r-2-oxathiacyclopenta-3-ene 2-
oxide (243): mp 129-131°; ir (KBr) 710, 748, 768, 1450, 1495, 1600 (phenyl), 1630, 3035, 3060, 3070 (C=C) and 1125 (sulfinate) cm⁻¹; pmr (CDCl₃) δ 6.39 (d, 1, S-0-CH, J = 2
Hz), 6.73 (d, 1, =CH; J = 2 Hz), 7.48 (m, 10, phenyl) ppm; mass spect. m/e 208 (M-SO).

Anal. Calcd. for C_{15}H_{12}O_{2}S: C, 70.28; H, 4.72; S, 12.50. Found: C, 70.12; H, 4.64; S, 12.51.

3,5-5-Diphenyl-1,2-oxathiacyclopenta-3-ene 2-oxide (244): mp 130-132°; ir (KBr) 705, 735, 745, 770, 1450, 1495, 1600 (phenyl'), 1630, 3030, 3060 (C=C), 1125 (sulfinate) cm^{-1}; pmr (CDCl_{3}) δ 6.80 (d, 1, =CH, J = 2 Hz), 6.90 (s, 1, S-O-CH, J = 2 Hz), 7.50 (m, 10, phenyl) ppm; mass spect. m/e 208 (M-SO).

Anal. Calcd. for C_{15}H_{12}O_{2}S: C, 70.28; H, 4.72; S, 12.50. Found: C, 70.17; H, 4.78; S, 12.51.

In two similar experiments, 227 was reacted with concentrated sulfuric acid at 0° and at room temperature. In both cases the same isomeric sulfinites were obtained.

In one experiment, absolute ethanol was used as diluent. A solution of 0.2 gm (0.00078 mole) of 227 dissolved in concentrated sulfuric acid (2 ml) was cooled to -7°C and diluted with 15 ml of absolute ethanol. The slightly brown solution was neutralized with sodium bicarbonate. The mixture was then filtered, the yellow filtrate evaporated under reduced pressure and the residue dried in vacuo. Infrared spectra showed that this residue was a mixture of the same sulfinites.

The concentration of sulfuric acid required for the reaction was investigated. 2,4-Diphenylthiete 1,1-di-
oxide (227) was soluble in the concentrated but not the dilute sulfuric acid. Therefore a suspension was used. Stirring a suspension of (227) in 70% (w/w) sulfuric acid for 22 hours or heating the mixture at 50° for one hour resulted in the recovery of the starting material. Again no reaction was observed when 227 was dissolved in a mixture containing organic solvent (acetone or benzene) and 60% or 70% aqueous sulfuric acid.

No reaction was observed when 2-phenylthiete 1,1-dioxide (272) (85) or 2-phenyl-4-methylthiete 1,1-dioxide (273) (85) was treated with concentrated sulfuric acid. Heating a mixture of concentrated sulfuric acid and 272 at 50-60° for ½ hour also resulted in recovery of unchanged starting material.

26. Attempted hydroboration of 2,4-diphenylthiete 1,1-dioxide (227).

A solution of 227 (0.5 gm, 0.002 mole) in 25 ml of dried tetrahydrofuran was cooled in an ice bath, swept with dried nitrogen and treated with 0.012 mole of diborane in 20 ml of dried tetrahydrofuran. The resulting mixture was swept with dried nitrogen, stoppered and then stirred overnight. The excess diborane was carefully destroyed by adding 5 ml of water and 3 ml of chromic acid (prepared by dissolving 5.5 gm of sodium dichromate in a mixture of 4.2 ml concentrated sulfuric acid and 24 ml of
water) was added in. The reaction mixture was refluxed on a steam bath for 1/2 hour and the solvent was removed by evaporation. The residue was extracted with chloroform. The chloroform solution was washed with water, dried over anhydrous sodium sulfate and evaporated to give 0.4 gm of liquid. A small amount of ether was added and the solid (0.15 gm, 73%) that appeared was collected by filtration. The ir spectrum indicated that it was unchanged. The ethereal filtrate was evaporated to an oily liquid. Tlc and ir data showed that it was a crude mixture of several components, containing unreacted and other substances. No desired product was detected.

27. Synthesis of 2,2-dichlorophenylacetyl chloride (282).

2,2-Dichlorophenylacetyl chloride was prepared according to a method adopted from the literature (117). A mixture of phosphorous pentachloride (567 gm, 2.72 mole) and phenylacetyl chloride (209 gm, 1.36 mole) was refluxed at 140° for 36 hours. The resulting mixture was distilled at 73-76° to give 311 gm of phosphorous trichloride, a reaction by-product. The residual liquid was then distilled in vacuo to yield 262 gm (85%) of 282, bp 110-115° (8 mm) (lit. (117) 102-105° (6.5-7 mm); 90%).


N,N-diethyl-2,2-dichlorophenylacetamide (283)
was synthesized according to a known method (117). To a stirred and ice-cooled solution of 2,2-dichlorophenyl-acetyl chloride (254 gm, 1.14 mole) in one liter of dried benzene, diethylamine (170 gm, 2.36 mole) was introduced dropwise from a pressure-equalizing addition funnel. After stirring at ice temperature overnight, the solution was filtered and evaporated to give a yellow liquid which was distilled in vacuo to yield 251 gm (85%) of 283, bp 120° (0.05 mm) (lit. (117) 142-144° (1.3 mm); 50%); ir (neat) 1665 (carbonyl) cm⁻¹.

29. Synthesis of N,N-diethyl-α,β-dichloro-β-styrylamine (284).

The method was adopted from the literature (117). A mixture of N,N-diethyl-2,2-dichlorophenylacetamide (283) (52 gm, 0.2 mole) and tri-n-butylphosphine (41 gm, 0.2 mole), under a stream of dried nitrogen, was heated on a steam bath for one hour. The slightly brown liquid was distilled in vacuo. The fraction boiling at 103-106° (0.04 mm) was collected. Redistillation of this crude product gave a colorless product (284) bp 81-83° (0.03 mm) (lit. (117) 90-92° (0.1 mm)); ir (neat) absence of carbonyl absorption.


The preparation of the title compound was carried out according to a known procedure (179). Butyl
lithium (0.14 mole) in 82 ml of dried benzene was stirred under a stream of dried nitrogen and cooled to -10°. A solution of N,N-diethyl-α,β-dichloro-β-styrylamine (284) (30 gm, 0.125 mole) in 18 ml of dried benzene was added dropwise from a stoppered pressure-equalizing dropping funnel, the temperature of the reacting mixture being maintained at -10°. After the addition had been completed, the reacting mixture was placed at room temperature and stirred for one more hour. The brown turbid mixture was centrifuged, the supernatant was separated with the aid of more benzene and the solution was evaporated under reduced pressure to a brown liquid. Purification by vacuum distillation yielded 13.3 gm (72%) of pure 285, bp 78° (0.03 mm) (lit. (179) 75° (0.2 mm), 85%); ir (neat) 698, 765, 1440, 1580, 3050 (phenyl) and 2210 (acetylene) cm⁻¹; pmr (neat) δ 1.16 (t, 6, CH₃, J = 7 Hz), 2.82 (q, 4, CH₂, J = 7 Hz) and 6.98-7.45 (m, 5, phenyl protons) ppm.

31. Synthesis of 2,4-diphenyl-3-diethylaminothiete 1,1-dioxide (231).

This compound was prepared according to a procedure taken from the literature (200). A solution of benzylsulfonyl chloride (0.57 gm, 0.003 mole) in 10 ml of dried acetonitrile was added dropwise to a stirred and ice-cooled mixture of triethylamine (0.39 gm, 0.003 mole), N,N-diethylphenylethynylamine (0.51 gm, 0.003 mole) and 30 ml of
dried acetonitrile. The resulting solution was stirred in the ice bath for 18 hours, filtered and evaporated to a residue which was redissolved in tetrahydrofuran. The insoluble hydrochloride was removed by filtration. The filtrate was evaporated to give 0.55 gm (56%) of solid product which was recrystallized from ethyl acetate to yield 0.4 gm of crystalline 2,4-diphenyl-3-diethylaminothiete 1,1-dioxide (231), mp 142-144° (lit. (185) 143-144°); ir (KBr) 720, 780, 790, 1470, 1505, 3070 (phenyl), 1165, 1130 (sulfone), 1625 (enamine) cm⁻¹; pmr (CDCl₃) δ 0.85 (t, 6, CH₃, J = 7 Hz), 3.03 (q, 4, CH₂, J = 7 Hz), 5.73 (s, 1, SCH), and 7.15-7.65 (m, 10, phenyl) ppm.

32. Attempted hydrolysis of 2,4-diphenyl-3-diethylaminothiete 1,1-dioxide (231).

A suspension of water-insoluble 2,4-diphenyl-3-diethylaminothiete 1,1-dioxide (231), 5 ml of water and 2.5 gm of sulfonic acid resin (BIO-RAD AG50W-X8) was stirred for 3 hours. The resulting aqueous mixture was extracted with chloroform. Evaporation of the chloroform solution resulted in quantitative recovery of the unchanged 231.

Repeating the experiment by using Amberlite 120 resin gave the same result.

In one experiment 231 was dissolved in a mixture of acetone and 5% hydrochloric acid. The solution was re-
fluxed on a steam bath for three hours and then placed aside at room temperature for three weeks. Work-up also resulted in the recovery of unchanged 231.

2,4-Diphenyl-3-diethylaminothiete 1,1-dioxide (231) was also recovered unchanged from a concentrated hydrochloric acid suspension after stirring at room temperature for one week, or from a solution made of concentrated hydrochloric acid and a minimum amount of acetone.


158. B. Loev and M. Goodman, Chem. and Ind. (London), 2026 (1967).


